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EDITORIAL

Treatment of Pancreatitis

THE CURRENT treatment of pancreatitis is largely related to current attitudes as to the etiology of the disease. A clear relationship has been established between cholecystitis and pancreatitis. Reflux of bile into the pancreatic ducts or partial obstruction to outflowing pancreatic juice due to spasm or stricture of the sphincter of Oddi were thought to be possible etiologic factors. Sphincterotomy, removal of calculi, drainage of the tail of the pancreas through the jejunum, side to side anastomosis of the pancreatic ducts to the jejunum and resection of the pancreas have all been performed.

Sympathectomy and splanchnicectomy have been performed in an attempt to eliminate spasm of the sphincter. Others have believed that cutting the sphincter might be more effective. While section of the nerves did relieve pain and symptoms in some patients and sphincterotomy was effective in others, there has been a large group of patients who have not been improved by sphincterotomy. Partial obstruction of outflow of pancreatic juice at a point higher up in the duct system has been found in some of these patients. This blockage commonly consists of a single calculus lodged 3 to 5 cm. above the ampulla of Vater or at the bifurcation of the ducts of Santorini and Wirsung. A calculus which has been lodged at one of these points for a period of time may erode the duct wall and, thus, indirectly cause stricture formation at that point. Gradual movement of such a calculus down the duct from the bifurcation of the ducts to the pancreatic sphincter of Boyden (3 cm. above the ampulla of Vater) could theoretically cause multiple strictures to form.

It is essential either to explore the pancreatic ducts with a probe or to execute a pancreatogram in order to learn whether or not there is stone or stricture in the ducts. If the pancreatic duct cannot be identified after stimulation of flow with secretin, the tail should be transected and retrograde exploration or pancreatography performed. Therapy for a patient with clear ducts above the ampulla should be sphincterotomy alone. Calculi, easily removable through the ampulla after sphincterotomy, should be removed with forceps or ureteral basket, at which time a plastic drainage tube should be placed in the pancreatic ducts and the fluid drained to the outside. The juice thus collected should be fed back to the patient. This tube should be removed two weeks postoperatively.

Patients with one or two strictures can be treated by the tail drainage Roux–Y procedure advocated by Aird, DuVal and Puestow. Those with multiple strictures with intervening duct lakes should have the strictured pancreatic duct filleted, using the method of Puestow and Gillesby, and a side to side anastomosis of the jejunum to the duct performed. Following these procedures, distention of segments of the pancreatic duct after meals with resultant pain should disappear; furthermore, the normal flow of digestive enzymes into the intestinal tract should be restored with improvement in absorption. *It is apparent that an operation for relief of obstruction must be tailored to the situation.* Resection should be performed only after all the aforementioned methods have failed.

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Thyroglossal Duct Cysts and Sinuses: Results of Radical (Sistrunk) Operation

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IT HAS been more than thirty years since Sistrunk [5] reported on the results of his operative technic for dealing with thyroglossal duct cysts and sinuses and twenty years since Pemberton and Stalker [4] reported the results of such treatment. Although it has been accepted generally that the Sistrunk operation is indicated as the method of treatment for most thyroglossal duct cysts and sinuses, a surprisingly large number of patients admitted for surgery have a history of multiple surgical attempts which have failed to produce a cure.

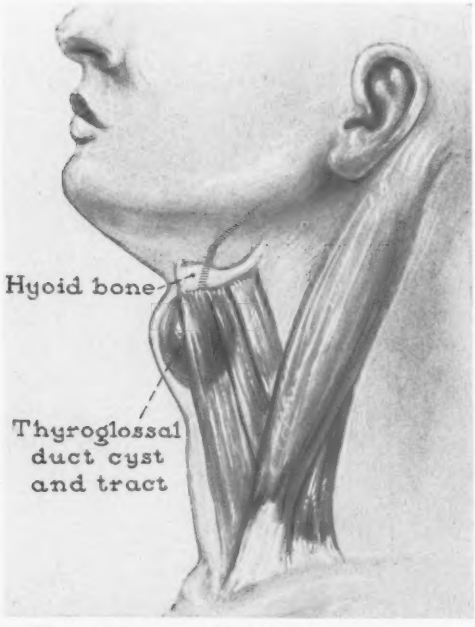

FIG. 1. Ordinary relationships of cyst and tract.

EMBRYOLOGY

For present purposes, the important embryologic feature is the downward projection of the thyroidal anlage from the region of the foramen cecum of the tongue in the human embryo of 2 to 2.5 mm. As development progresses, the thyroidal substance descends to its position in the anterior part of the neck. In the normal course, the connections between the cervically placed thyroid and its point of origin at the foramen cecum disappear. When this midline tract or sinus remains, it is lined by epithelium previously carried downward with the descent of the thyroid. The thyroglossal tract passes through or near the center of the second branchial arch which has elaborated the hyoid bone. A cyst can form at any point along the tract, but the usual location is under the skin just above or below the hyoid bone. (Fig. 1.)

External fistulous openings, originating from the thyroglossal duct or tract, are always considered a secondary feature because normally the duct does not communicate with the outside [2]. Such openings are marks of surgical drainage or incomplete removal.

The purpose of this paper is to emphasize the fact that the entire sinus tract must be removed. It is perhaps best achieved by a review of our surgical experience in a fifteen year period since the report of Pemberton and Stalker [4], a review of the surgical anatomy and an analysis of the causes of recurrence.

Material and Methods. The files of the Mayo Clinic for the fifteen year period from 1939 through 1953 were examined for all records of cases indicating a clinical diagnosis of thyroglossal duct sinus or cyst. Among the 600 cases studied were forty-four in which the clinically diagnosed thyroglossal process proved at operation to be some other abnormality of the neck. These cases were not included in the present study. In another group of 175 cases, surgical treatment was not carried out. In a third group of 381 cases, pathologic examination of tissues confirmed the diagnosis of thyroglossal duct sinus or cyst. Follow-up information was obtained for the patients of the latter two groups.

TABLE 1
INCIDENCE OF THYROGLOSSAL DUCT CYSTS AND SINUSES ACCORDING TO AGE AND SEX IN 381 SURGICAL CASES

Age (yr.)	No. of Male Patients	No. of Female Patients	Total
0 to 9	40	32	72
10 to 19	50	39	89
20 to 29	22	20	42
30 to 39	37	35	72
40 to 49	35	20	55
50 to 59	19	14	33
60 to 69	8	7	15
>69	3	0	3
Total.....	214	167	381

PATHOLOGY

The usual thyroglossal duct specimen is composed of a cyst of variable size attached to a tract of 4 to 6 cm. which has coursed close to the hyoid bone. Sometimes, only the fistulous tract remains, devoid of lining but with a variable amount of surrounding inflammatory reaction. Among the 381 patients whose diagnosis was confirmed by pathologic examination of surgical specimens, 221 patients had, on admission, a cystic lesion just above or below the hyoid bone, associated with a tract as just described. The remaining 160 patients, however, had, on admission, a draining or quiescent sinus at or slightly below the hyoid bone.

The diameter of the cysts ranged from 2 to 4 cm. (usual) up to 6 to 8 cm. (rare). The largest measured 8 by 8 by 10 cm.

The mucosal linings of the cysts and sinuses were essentially similar. Squamous epithelium was mentioned eighty times, transitional epithelium twelve times, cuboidal epithelium four times, and ciliated and columnar epithelium eighty-nine times. In only one cyst was there papillary infolding. The mucosal lining in the remaining specimens was obliterated, for the most part, by inflammation or fibrous changes. In six specimens, microscopic examination of the lining of the cyst or duct showed associated thyroid tissue. Grossly, however, an attachment of the pyramidal lobe to the thyroglossal duct had necessitated its incidental removal in ten cases.

DIAGNOSIS

Age and Sex. There were 214 male patients and 167 female patients in the group of 381 who received surgical treatment. These cases were heavily distributed through the first five decades of life. Only fifty-one patients beyond fifty years of age were included (Table 1), whereas seventy-two were less than ten years of age and two of these were less than fifteen months old.

Site of Sinus or Cyst. About ninety per cent of the sinuses were located in the midline. Eleven lesions were to the right of the midline and twenty-nine were to the left of it. Most of those patients, who had laterally placed sinuses, had a history of at least one previous operation. In a few cases of laterally placed sinus in patients not previously examined elsewhere, the diagnostic possibility of branchial cleft sinus was considered.

It is interesting that on admission twenty-two patients had sinuses on the midline at various points below the hyoid bone; twelve of these were at or above the sternal notch or over the upper sternum.

In those patients who were admitted because of cysts, the location of the lesions was usually at or near the hyoid bone or slightly cephalad. Intermittent increase and decrease in the size of the cyst was common; however, a few patients mentioned progressive enlargement. A few patients also had noted, sometimes, a peculiar taste in the mouth, often associated with a decrease in the size of the cyst. On occasion, laryngoscopy was performed and proved helpful in verifying the diagnosis. Only four patients were admitted because of a cystic mass or sinus tract on the posterior tongue at the foramen cecum. (Fig. 2.) Two of these were treated by excision of the lesion via the oral route.

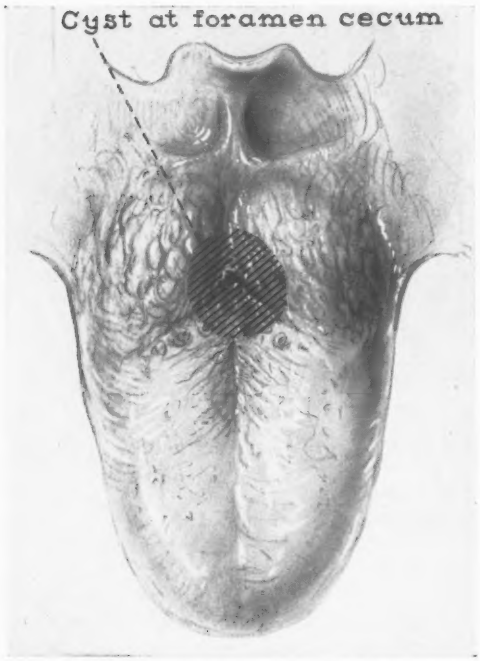

FIG. 2. Extremely unusual location of cyst.

Duration of Symptoms Prior to Treatment. Of the 381 patients operated on, 187 had experienced the onset of symptoms or signs relative to their thyroglossal duct cyst or sinus before their sixteenth birthday. Of the 175 patients not operated on, forty-four had had onset of symptoms before sixteen years of age. The duration of symptoms prior to operation at the Mayo Clinic was extremely variable. Regarding the cases in which there was no previous attempt at therapy, our analysis suggested that, in general, the interval between the onset of symptoms and curative surgical treatment by the Sistrunk procedure was relatively short, usually a matter of months. Generally, the other patients had a history of a long interval from the time of onset of symptoms until curative operation; in the majority of instances it was a matter of years. This long period usually had been punctuated by numerous surgical attempts followed by recurrent bouts of infection and intermittent drainage from sinuses or a postoperative fistula in the region of the hyoid bone.

The cases in which surgery had not been performed before totaled 202. Among the 179 others, 191 attempted excisions and 124 incisions or drainage procedures were recorded. Two patients had had six surgical attempts previously, three patients had had five surgical attempts and two patients had had four such failures.

TABLE II
PREVIOUS SURGICAL PROCEDURES AND ATTEMPTS AT TREATMENT OF 381 SURGICAL PATIENTS WITH THYROGLOSSAL DUCT CYST OR SINUS

Previous Procedures	Patients with Cysts (221)	Patients with Sinuses (160)	Total
Attempted excision....	58	133	191
Incision and drainage..	39	85	124
Silver nitrate cautery, electrocautery.....	6	8	14
Aspiration.....	7	7	14
Roentgen therapy.....	3	3	6

Table II shows that among the 221 surgical patients who were admitted for thyroglossal duct cysts there had been ninety-seven previous surgical failures; whereas, among the 160 surgical patients who were admitted because of a sinus or fistula, there had been 218 previous surgical attempts. The data suggest that the sinuses and fistulas, more than the cysts, moved physicians to treat repeatedly. Some patients had received a variety of other treatments: aspiration was recorded fourteen times, cautery with silver nitrate and various other agents had been tried fourteen times and roentgen therapy had been tried six times.

It is of interest that in seventeen cases, the thyroglossal duct cyst was asymptomatic and was found only incidentally during physical examination. The remaining 364 patients came to the clinic with a chief complaint referable to the thyroglossal problem, except for fourteen patients who underwent radical thyroglossal surgery coincidental to removal of laryngeal carcinoma or thyroidal adenoma.

Differential Diagnosis. Although the diagnosis usually was not difficult, the operative findings did not support the clinical diagnosis of thyroglossal duct cyst or sinus in forty-four instances already mentioned. Among these forty-four cases, Sistrunk procedures were performed in four in which the diagnosis was not clear even at operation. Pyramidal lobe or midline thyroid adenoma proved to be the correct diagnosis in twenty-four other instances,

branchial cleft cysts or sinuses were present in seven, inflammatory lymph nodes were found in four, lipomas in three and Boeck's sarcoid in a lymph node was found once. These were the reasons for excluding the forty-four cases from further study.

MANAGEMENT

Surgical Management. Sistrunk operations were performed in 350 (92 per cent) of the 381 cases in which the patients were treated surgically. In only thirty-one cases of surgery in this study was the central portion of the hyoid bone not removed. There were several reasons for not resecting the bone in these patients.

As mentioned, fourteen of these patients had the thyroglossal duct removed coincidentally during laryngeal operations for carcinoma (seven patients) or thyroidal adenoma (seven patients), and the dissection was stopped at the hyoid bone. Another seven patients had had the hyoid bone resected in the course of previous surgical attempts performed elsewhere. At the Clinic, two patients had an operation which was limited to an oral approach and two had only a biopsy of the thyroglossal cyst wall. One patient was treated by incision and drainage and was instructed to return for a Sistrunk procedure, which he did not do. Of the remaining six patients who did not have the central portion of the hyoid bone removed, all suffered recurrence.

In examining the reports of the seven cases in which resection of the hyoid bone had been performed elsewhere, it is important to note that in none of the other 172 cases, making up the group of 179 with 315 previous surgical procedures, had the hyoid bone been removed. In other words, 96 per cent of the patients we have seen for recurrence, after surgical attempts were made elsewhere, had not had removal of even a segment of the hyoid bone.

Four patients were admitted with a chief complaint referable to the region of the foramen cecum. Two of these patients were treated by the Sistrunk procedure and two by intraoral approaches only, with deep wedge excision of a sinus tract in the foramen-cecum region of one and incision and electrocoagulation of cystic tissue in the foramen cecum in the other.

Nonsurgical Management. Of the thyroglossal duct cysts or sinuses in the 175 patients who were not admitted for surgery *per se*, the great majority were discovered incidentally in the course of a routine examination or at the time of evaluation for other conditions. For the most part, they were asymptomatic.

TABLE III
REASONS FOR NOT OPERATING IN CASES OF THYROGLOSSAL DUCT CYST AND SINUS

Reason	Cases
Operation advised or optional: patient refused.	77
Operation not advised	
Associated medical problem	33
Symptoms minimal or absent	39
Delay suggested (infancy, infection, other)	26
Total	175
(Eventual operation elsewhere among 105 cases traced)	(23)

The reasons given for not treating surgically patients with this problem, which is generally accepted as surgical, are outlined in Table III. It is important to note that none of the 175 have returned to the Mayo Clinic for surgery and that follow-up letters from 105 persons in this group (61 per cent) have revealed that twenty-three (22 per cent) of these needed subsequent operation. It is true that the clinical impression could have been in error in some instances; however, the diagnosis was confirmed in every instance in which surgical treatment was carried out elsewhere.

Of the 381 patients who received surgical treatment at the Clinic, only eighteen (5 per cent) had been seen here previously for problems involving the thyroglossal duct and returned for surgical treatment as recommended. Of these, seven had had acutely inflamed thyroglossal ducts or sinuses, and surgery had been delayed intentionally for up to three months until the infection subsided. Another six required incision and drainage followed by a delay for the inflammation to subside, and one more such patient never returned after incision and drainage. Two patients, infants when first seen, were brought back when they were older (eight and twelve years old, respectively) as recommended. In another case, surgery was not advised because of associated medical problems; but the symptoms of thyroglossal duct sinus intensified, necessitating a definitive operation. One patient refused surgery but returned for such treatment twelve years later.

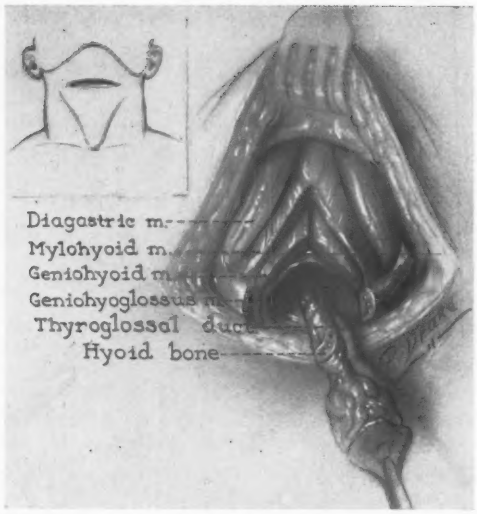

FIG. 3. Location of incision. Dissection of cyst and sinus; section of hyoid bone; and coring out of tongue muscle.

TECHNIC OF OPERATION

A transverse (4.5 cm.) incision directly over the cyst gives good exposure. (Fig. 3.) A vertical incision should be avoided, for the scar that results is oftentimes unsightly and may even produce a midline contracture. If the cyst has ruptured or if surgery has been attempted previously and the sinus presents at or near the hyoid bone, an elliptic transverse incision should be made around the tract. Although Sistrunk initially suggested the injection of a weak solution of methylene blue into the sinus tract in order to outline its course more definitely, this is no longer thought to be necessary.

Taut traction of the skin edges with sharp retractors provides adequate exposure while the cyst or sinus tract is being dissected from its point between the sternohyoid muscles and their attachment to the hyoid bone. Wide dissection of the tract should be carried out toward the hyoid bone, staying well outside the cyst and any inflammatory zone. Although the tract may pass underneath the bone, it may pass superficially to it or through it. This possibility necessitates removal of a central segment of hyoid bone 1 to 2 cm. long. (Fig. 3.)

Often the tract may be broken or may become only an atretic fibrous band at or just above the hyoid bone. The inexperienced surgeon is inclined to ligate the tract either inferior to or just above the hyoid bone, with the belief that he has performed an adequate procedure. Dissection must be carried out to the foramen cecum, however, which is identified by the surgeon's left index finger in the patient's mouth, palpating backward along the two rows of circumvallate papillae on each side of the tongue; the foramen will be found at the point where these rows approach the midline. (Fig. 4.) Once the foramen cecum has been stabilized by forward and upward pressure with the intraoral finger, a 3 mm. to 5 mm. block through the geniohyoglossus and geniohyoid muscles should be carefully cored out. The dissection should be carried out to but not through the mucous membrane of the foramen cecum.

(Sistrunk made the point that the direction of the thyroglossal duct above the hyoid bone should be at a 45° angle to the horizontal position of the patient. This may vary considerably with bending of the neck, but with the foramen cecum as a guide, bimanual tactile exploration seldom leads to inadequate dissection.)

If the mucous membrane of the pharynx or foramen cecum is opened, it should be simply closed with interrupted sutures of fine catgut. The opening through the muscles of the tongue can be closed with interrupted catgut sutures through the periosteum of the hyoid bone, which will allow approximation if this is desired. (Fig. 4.) No ill effects have followed when the ends of the hyoid bone were left apart. Gross [1] made the point that there may be some hesitancy to carry out the dissection to completion in the depths of the wound for fear of entering the mouth. He pointed out, however, that the thyrohyoid membrane which is just beneath the muscles is distinctly grayish yellow, in contrast to the red muscle superficial to it. He suggested that the thyrohyoid membrane be exposed initially by puncturing the muscles at one point and then carrying a scissors dissection around in a circle to free the block of tissue that is considered adequate.

If the sinus occurs lower in the anterior part of the neck (as it did in approximately 10 per cent of the patients in this study), a separate initial transverse elliptic excision of the tract can be made, allowing a tunneling out of the tract subcutaneously up to a point near the hyoid bone where a second transverse incision can be made. The previously dissected tract then can be passed upward through the subcutaneous tunnel and the dissection carried out

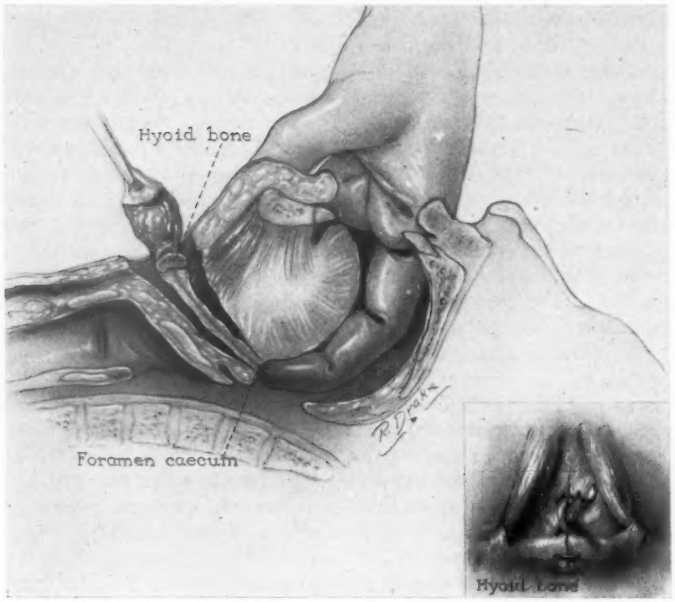

FIG. 4. Method of accurate identification of foramen cecum. Closure of periosteum and muscles.

in the aforementioned fashion. It is not necessary to drain the wound if hemostasis has been adequate and if inflammation has been minimal; otherwise, a small soft drain should be left in place for thirty-six hours.

RESULTS OF TREATMENT

Information obtained by follow-up, as of January 1, 1958, is available for 367 (96 per cent) of the 381 patients operated on at the Mayo Clinic. (Table IV.) Of these 367 patients, 351 (96 per cent) have been free of evidence of recurrence of thyroglossal duct symptoms for at least five years.

Recurrence. Sixteen patients (4 per cent of the traced patients of the surgical group) received treatment for recurrence during the follow-up period of this study. Ten patients returned to the Mayo Clinic for treatment of recurrence. Among the six cases of recurrence disclosed by follow-up letters, five patients underwent an additional operative procedure and the other is under a physician's care. Of the patients who had a recurrence following operation at the Mayo Clinic, eight of the ten recurrences were in patients who had had previous surgical attempts before being treated at the Clinic. Six of these eight did not have a segment of hyoid bone removed by us, since it had been performed elsewhere. However, a wider segment of bone was removed in several instances at reoperation.

TABLE IV
RESULTS OF OPERATIVE AND OF NONOPERATIVE TREATMENT FOR THYROGLOSSAL DUCT CYST AND SINUS

Treatment	No. of Patients (total of 556)	Per cent
Operative treatment	381	...
Number traced	270	71
Known free of symptoms for at least five years	254	94*
Recurrences	16	6
Treated at Mayo Clinic	10	...
Disclosed on follow-up	6	...
Complications	7	...
Mortality	0	0
Nonoperative treatment	175	...
Number traced	105	61
Known to have had continued symptoms	24	...
Required operation elsewhere later	23	... 22*
Recurrence after operation	5	...
Mortality	0	0

* Based on traced group as of April 1, 1960.

Of the two patients who had not had surgical attempts previously, one had had only a biopsy as the initial procedure; accumulation of fluid necessitating continued drainage made a more complete operation obligatory. One other had been treated initially with a classic Sistrunk operation, but recurrence required another operation five years later. No reason for this recurrence could be found.

In only one patient was the hyoid bone left intact at the time of operation for recurrence. Fluid began to accumulate and continued drainage became necessary. This patient finally was treated successfully by the classic Sistrunk procedure.

Of the ten patients just discussed, none has had further recurrence. Of the six patients who were found, by follow-up letter, to have had recurrence, five had a problem of recurrence when they came to us for the first time. One of these did not have a segment of hyoid bone removed at the time of operation at the Mayo Clinic. One had only an incision and drainage for an acute thyroglossal infection and was instructed to return for excision when it had subsided. She failed to do so, and wrote of numerous trials of incision and drainage and of attempts at excision elsewhere in 1954 and 1958.

Thus, although there were sixteen cases with recurrence, only one lacked evidence of a prior inadequate surgical attempt; this was the only recurrence known to have developed, after adequate initial treatment, without any apparent cause other than technical factors.

Complications. In seven patients, complications developed as the result of surgery. One adult, whose oral cavity was entered (and closed in the fashion described under the section on technic), had transient edema of the epiglottis. One was noted at reoperation to have low grade osteomyelitis in the ends of the hyoid bone; however, the patient has had no further difficulty. One had an abscess from stitches (that receded) spontaneously. One had transient low grade cellulitis. Two had a small abscess in the incision several weeks after operation; but in both cases the response to incision and drainage was good and both patients have remained well since. The seventh patient suffered a temporary loss of function of the glossopharyngeal nerve on one side; in five months the nerve function was normal. In the entire series there were no deaths referable to the surgical treatment.

COMMENTS

The interposition of the hyoid bone at the mid-point in the course of the thyroglossal tract is an unhappy embryologic coincidence that may pose a problem to the surgeon. Those who have had the opportunity of operating on the thyroglossal tract a number of times will recall the occasional instance in which the tract above the hyoid bone does not persist as a well defined structure. For this reason, the surgeon is often tempted to stop the dissection once the hyoid bone has been reached. The temptation is especially strong if the exposure has been less than perfect or if anesthesia has been less than ideal during the operation. However, with no exception, one should remove the central segment of hyoid bone and continue the corelike dissection of the tract and some of the surrounding muscle upward to the floor of the foramen cecum.

Although the great majority of patients have cysts or sinuses in close relationship to the hyoid bone, almost six per cent of the patients in our series had midline sinuses some distance below the hyoid bone. Half of these were at or just above the sternal notch. Because the tracts continued upward to the foramen cecum, we believed they did not represent the midline cervical clefts described by Gross [*1*]. A second transverse incision aided materially in the dissection and total removal of these long tracts.

We did not encounter the rare situation in which all of the patient's thyroid gland is contained in a midline mass near the hyoid bone or base of the tongue. It seems that in such instances the absence of a tract leading superiorly and the solidity of the apparent cyst would arouse the suspicion of the surgeon.

Our clinical opinion that not all thyroglossal duct cysts and sinuses require surgery is supported by the information obtained by follow-up of the 175 patients who, for various reasons, did not undergo surgical treatment; many of them have been free of symptoms. However, about 22 per cent of those traced have been operated on subsequently. The prognosis for a cyst may not hold for a sinus; almost inevitably with the latter there will be intermittent accumulation of fluid or bouts of inflammation, or both. As a rule, patients having thyroglossal sinuses reported more previous unsuccessful attempts at treatment than did those having thyroglossal duct cysts.

Many patients called their disorder by name. Some patients had at least a superficial knowledge of its embryology and a few sensed the aspect of "medical curiosity" of such tracts and sinuses. But despite these indications that the entity had been properly recognized, it was recurrent following attempts at surgical treatment in 179 patients (32 per cent) who were first admitted with a thyroglossal duct cyst or sinus. This does indicate improvement from the 57 per cent recurrence rate among the 293 patients reported by Pemberton and Stalker in 1940.

In only thirty-two (8 per cent) of the 381 patients treated surgically at the Clinic was the central segment of the hyoid bone left intact. The diagnosis of thyroglossal duct was incidental to operation for laryngeal carcinoma or thyroidal adenoma in fourteen of these thirty-two patients.

Only for six among them was there no secondary reason for failure to remove the hyoid bone, and all six suffered recurrence. In contrast, among the 179 cases with 315 prior surgical procedures, only seven patients had had resection of the central portion of the hyoid bone as a part of the procedures performed previously. From these observations, we believe it essential to the complete removal and the successful treatment of the thyroglossal apparatus that a central segment of hyoid bone be removed in the course of dissection.

Of the sixteen patients with recurrence, fifteen had a history of one or more unsuccessful surgical attempts. In only one instance following a Sistrunk procedure was there recurrence in a patient who had an uncomplicated form of the disease which was treated for the first time at the Clinic and for which no cause was apparent.

Obviously, the best time to perform a definitive Sistrunk operation for thyroglossal duct cyst and sinus is initially, once surgical intervention has been decided. Probably the only exception to this rule might be made when an acutely inflamed cyst needs incision and drainage. In such an instance, removal of the duct should be postponed until the inflammatory reaction has subsided.

If the cyst becomes evident in infancy or early childhood and if it is asymptomatic, we believe the Sistrunk procedure should be postponed until the child's airway is large enough and the cartilage rigid enough to obviate any need for tracheotomy in the immediate postoperative period. Nearly half of the patients had onset of their symptoms before their sixteenth birthday, yet only 30 per cent of them were operated on before they had reached that age. We believe the most favorable age for excision of those thyroglossal cysts and sinuses which occur in childhood is in the range of seven to ten years; elective removal during a school vacation period may be the optimal course.

Other than infancy, only concurrent medical conditions that would not permit the use of anesthetic agents would justify postponement of definitive operation for the patient with symptoms. Although the risk of the development of cancer approaches zero [3], the possibility of the subsequent development of symptoms should be explained in detail to the patient if he elects to defer operation.

SUMMARY

A group of 556 patients with thyroglossal duct cyst or sinus was studied. Radical operation (the Sistrunk procedure) had been performed in 381 cases.

Four per cent of the 270 surgical patients traced for five or more years had recurrence, but only one of these had not been subjected to some type of surgical attempt at treatment previously.

Among 105 traced patients not treated surgically when examined at the Mayo Clinic twenty-three later underwent operation elsewhere. The operative technic used at the Clinic is reviewed in detail.

The importance of removing the entire tract by the Sistrunk method, including the central portion of hyoid bone, is emphasized.

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Aneurysms of the Sinus of Valsalva

THREE DIFFERENT CLINICAL PICTURES

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ANEURYSMS of the sinus of Valsalva may occur as asymptomatic curiosities or they may open into one of the chambers of the heart, producing aorticocardiac fistulas. These lesions are rare [*14*]; only about fifty patients with ruptured aneurysms are reported in the literature and only a few patients have survived definitive surgery [*2,7,8,10,11,15*]. The three cases reported herein illustrate variations of the clinical course and surgical attack.

It is obvious that some, if not all, of these aneurysms are congenital [*2,12*]. Although it has been stated that the syndrome never occurs in infants and young children, there are at least four cases of children in the literature [*5*]. Our Case II is the youngest ever described; the murmur was found at birth and the lesion was verified during surgery when the patient was seven weeks of age. Explanation of a congenital origin is difficult. There are several theories, among which are the following: (A) failure of fusion of the central portion of the distal bulbar septum [*9*]; and (B) a "tear" of the elastic media from its attachment to the annulus [*3*]. There are many reasons which make one unhappy to accept these explanations. The hypothesis advanced by Patten [*13*], that these fistulas represent persistence of fetal coronary arteries which communicate with the intertrabecular spaces of the myocardium, seems more reasonable. We have extensive studies under way which are testing these theories and will be reported later. It appears that there is a close relationship between aneurysms of the sinus of Valsalva, especially with rupture, and various coronary artery anomalies, particularly fistulas.

In about half of the reported cases, the aneurysm has arisen in the right coronary sinus and communicated with the right ventricle. About 30 per cent arose in the noncoronary (posterior) sinus and opened into the right atrium. Two cases have arisen in the right coronary sinus and "ruptured" into the right ventricle and atrium. There are single reported cases of the following: (A) right coronary sinus to the pulmonary artery; (B) right coronary sinus to the left ventricle; (C) right coronary sinus to the pericardium; and (D) noncoronary sinus to the pericardium. About a dozen cases of unruptured aneurysms of the sinuses have been reported, and there have even been instances of aneurysms of all three sinuses.

Rupture typically occurs in adult life in a man who has had no previous indications of heart disease. There is frequently a clear history of a sudden onset of pain in the anterior portion of the chest, palpitation and weakness. These symptoms may subside shortly thereafter but are followed by the onset of unrelenting, progressive congestive heart failure. The patient usually dies of either heart failure or endocarditis within a year of onset. Physical examination usually reveals an enlarged heart, rales in the lung bases, hepatomegaly and dependent edema. The physical signs and blood pressure indicate aortic regurgitation, frequently together with signs of tricuspid insufficiency. The murmur, following rupture into the right ventricle is loud and harsh and is located along the lower left or right sternal border. It is best heard in the third or fourth intercostal spaces. The murmur seems superficial and reminds me of the quality of a severe aortic stenosis, except that it is continuous with diastolic accentuation or is even entirely diastolic.

Catheterization reveals an increase in the oxygen content of blood from one or both

chambers of the right side of the heart. Aortography may demonstrate the defect.

The presence of an aorticocardiac fistula is the indication for surgery. Numerous approaches to the surgical repair of this lesion have been attempted [*1,6,10,11*]. The best procedure appears to be "open heart" repair with extracorporeal circulation. Under these conditions, the lesion can be well delineated and repair of the aortic media to valve ring can be carried out. In the sick infant with a fistula which may be obliterated from the surface of the heart, closure without opening the heart is believed justified for it is safer although less satisfactory. If the fistula recurs in adult life, open heart surgery should be infinitely less risky at that time.

Three different surgical technics are illustrated in the following case reports.

CASE I. A forty-eight year old Negro man was admitted several years ago. He had a two month history of substernal fullness radiating to the epigastrium. There were no gastrointestinal symptoms. Physical examination revealed a blood pressure of 145/95 mm. Hg; otherwise, there were no abnormal findings.

The results of complete examination by both the gastroenterology and cardiovascular services were negative, except for histamine achlorhydria and left ventricular hypertrophy revealed by electrocardiogram. A roentgenogram of the chest showed a noticeably enlarged heart with a widened and dilated aorta; in addition, the esophagus was displaced to the right and anteriorly.

About one month after admission, at which time a diagnosis had not been established, the patient developed a diastolic aortic murmur. The region of the first portion of the aorta became more prominent and was obviously increasing in size. A clinical diagnosis of aneurysm of the sinus of Valsalva was made. This was confirmed by a percutaneous angiogram of the left ventricle.

Hypothermia was induced by a "lytic cocktail," and the esophageal temperature was lowered to 88°F. A 5 cm. aneurysm was found arising from the first portion of the right coronary sinus of Valsalva. (Fig. 1.) This aneurysm completely separated the interatrial plane. The aneurysm was dissected free and its neck was clamped; it was then removed and the aorta repaired. Just as the repair was completed, ventricular fibrillation developed in the heart. There was evidence of crushing of the right coronary artery by the clamp which probably precipitated the fibrillation.

CASE II. A Negro female infant was delivered by a twenty year old woman (para III, gravida III); there were no complications during pregnancy, labor or delivery. The infant weighed 6 pounds 12 ounces and was thought to have an enlarged heart and loud murmur at neonatal examination. Respiration was rapid throughout life and a cough was present from birth. The baby always vomited some of the milk after feeding.

At five weeks of age, the infant was still not well, although she weighed just over 7 pounds. Her pulse was 250 per minute with respirations of 50 per minute. The point of maximal intensity was in the sixth intercostal space in the anterior axillary line. There was a loud systolic murmur and thrill over the right sternal border with a loud P_2. The liver was enlarged to three fingerbreadths below the costal margin. An electrocardiogram revealed a sinus tachycardia with marked S-T elevation, increased intrinsicoid, depressed T waves in V_3, V_4 and V_5. These findings were interpreted as left ventricular preponderance and hypertrophy, and "strain pattern."

A percutaneous cardioangiogram of the left ventricle was executed on October 8, 1959, which revealed an enlarged left ventricle and suggestion of opacification of the right ventricle. The diagnosis of either aortic stenosis or ventricular septal defect was suggested.

The infant's condition continued to deteriorate over the next week, and it appeared that she would not tolerate the congenital lesion. Therefore, surgical exploration was advised. Hypothermia was induced to an esophageal temperature of 30°C. on December 15, 1959. The pump oxygenator was readied, but not primed.

A midline sternal-splitting incision was made and the heart was explored. There was a harsh diastolic thrill over the right ventricular outflow tract. In the region of the right coronary sinus, there was a 1 by 2 cm. thin-walled mass protruding from the sinus to the right ventricle, just below the pulmonary valve. (Fig. 2.) The right coronary artery arose adjacent to the aneurysm. The aneurysm was dissected from the coronary artery, and compression of the aneurysm caused the thrill to disappear and the right ventricle to immediately decrease in size. It was elected to attempt obliteration of the fistula by external suture to avoid the danger of extracorporeal circulation in a 7 pound infant. A clamp was placed across the base of the aneurysm and its convex surface opened. A probe was then passed from the aneurysm into the aorta just above the annulus and then from the aneurysm into the right ventricular outflow tract. This allowed clear confirmation of the fistulous connection between the aortic sinus and the right ventricle. The clamp was reapplied and a row of mattress sutures were placed along the neck of the aneurysm from the annulus to above the coronary ostium. After the clamp was removed, another row of

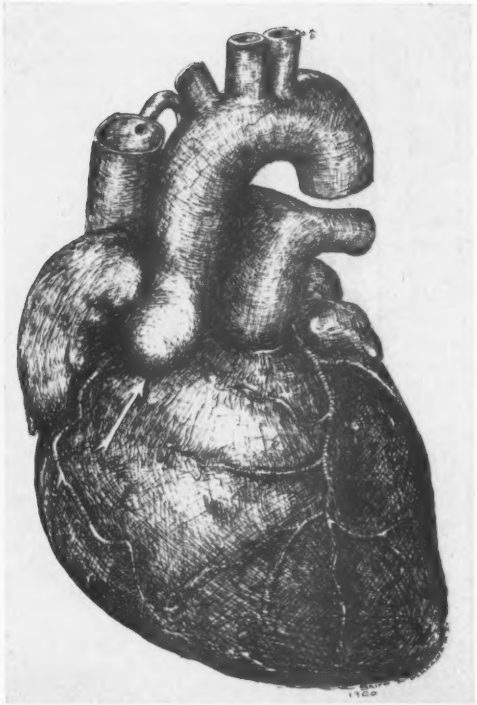

FIG. 1. The arrow indicates the unruptured aneurysm of the right coronary sinus of Valsalva (Case 1).

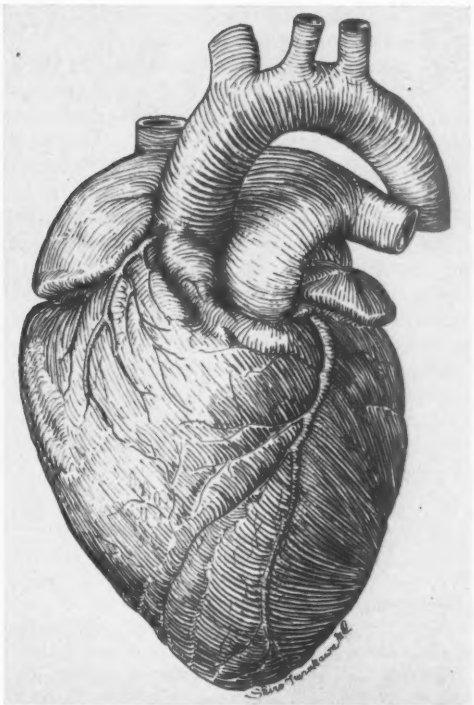

FIG. 2. The aneurysmal communication between the right coronary sinus of Valsalva and the right ventricular outflow tract is demonstrated (Case II).

sutures were placed deep to the first layer. The thrill was completely obliterated.

The postoperative course was extremely gratifying. The heart decreased in size rapidly, becoming normal, according to roentgenographic and physical examinations, by December 18, 1959. No murmur was heard after surgery and the liver was no longer palpable after three days. An electrocardiogram revealed a right bundle branch block pattern. The development of the infant has been good, and she remains asymptomatic.

CASE III. Our third patient was a thirty-one year old Negro man who suddenly developed severe dypsnea and pain in the left side of his chest on November 24, 1959. His past history was one of good health. He had had an appendectomy in 1956, at which time the blood pressure was 120/80 mm. Hg, and physical examination and x-ray films of his chest revealed no evidence of cardiac disease.

Physical examination three days later revealed marked distention of the veins in the neck, bounding peripheral pulses, obvious dyspnea with respirations of 44 per minute. The pulse rate was 104 per minute. There were many rales over both lungs. The heart was considerably enlarged with a particularly loud P_2. There was a peculiar loud harsh extremely superficial diastolic murmur along the right sternal border. The liver was enlarged to 4 cm. below the right costal margin and was pulsating. There was marked dependent edema. Venous pressure was 240 mm H_2O and the arm to tongue circulation time was 45 seconds.

The patient was immediately digitalized and given oxygen and mercurial diuretics which caused a slight improvement. The junior resident physician made a diagnosis of ruptured sinus of Valsalva aneurysm. On the day after admission, the temperature rose to 103°F.; numerous (fourteen) blood cultures, collected in the subsequent few days, were found sterile. Administration of Altafur® was initiated and a perirectal abscess was found. The abscess was opened causing prompt subsidence of the fever. On the sixth hospital day, jaundice, determined clinically, developed, and the hematocrit suddenly fell 10 per cent. Diagnostic studies revealed a glutathionine instability. The yellow pigmentation began to disappear gradually in the subsequent four days. Cardiac catheterization

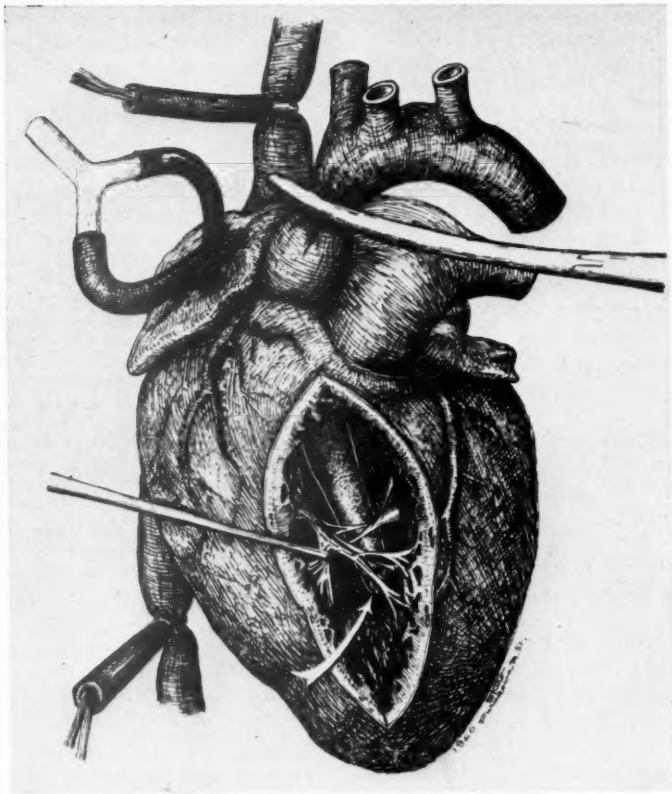

FIG. 3. Depicted above is the long finger-like projection of the aneurysm, with its ruptured tip, into the right ventricle (Case III).

showed a moderate elevation in right ventricular pressure and oxygen content.

On the fourteenth day of illness surgery was performed. A sternal-splitting incision was made and the disc pump oxygenator was connected to the patient. Average flow was maintained at 3,000 cc. per minute. The right ventricle was opened widely after asystole was induced by potassium citrate. There was a finger-like projection into the cavity of the ventricle. (Fig. 3.) This was adherent to the papillary muscles, the chordae tendinae and the septal leaflet of the tricuspid valve. There was a 1 by 1 cm. opening in the apex of the aneurysm from which arterial blood was pumping. After dissection, it was apparent that the aneurysm was pantaloon in type with a small protrusion into the atrium above the valve. The aneurysm was divided at its neck and removed. The defect in the aortic sinus was then sutured to the annulus. The defect into the atrium could not be completely closed through the tricuspid valve so the ventricle was closed and the right atrium opened. Use of four sutures promptly obliterated the fistula into the atrium. The atrium was then closed and extracorporeal circulation discontinued. The heart was open for fifty minutes with forty minutes of asystole. Total operating time was two hours and fifty-five minutes.

Plasma hemoglobin at the end of perfusion was 80 mg. per cent which is higher than is usually present. The heart began to function again without difficulty and the vital signs became normal. Within four hours of the time of surgery, there was obvious hemoglobinuria. The result of a Coombs test was negative. The hemoglobin and hematocrit remained normal and the gross hemoglobinuria disappeared after twenty hours. Glutathionine was 23 mg. per cent at this time (normal range, 50 to 100 mg. per cent). The patient ate a regular diet on the first postoperative day and his breathing was much improved, subjectively. He was given no medications other than penicillin and codeine postoperatively. One week after surgery his pulse was 84 per minute, blood pressure 100/70

mm. Hg, there were no murmurs present, his circulation time (arm to tongue) was 12 seconds and his venous pressure was 120 mm. H_2O. His condition has remained excellent.

COMMENTS

Case I was unusual in that there was no communication of the aneurysm with a cardiac chamber, the lesion was obviously increasing in size and the aneurysm was associated with cystic medial necrosis. In this case the aneurysm was probably acquired. The surgical approach demonstrates an extension of the "Søndergaard dissection" from the exterior of the heart to the fibrous skeleton of the annuli. While this procedure is interesting, it is now obsolete.

Review of the literature has revealed that Case II is by far the youngest patient with the syndrome. Since the lesion was present at birth, it was certainly congenital. The closed heart approach used in this instance, in conjunction with the dissection used in Case I, seems a valuable method for dealing with some lesions in the infant.

Case III is typical of ruptured sinus of Valsalva, its symptomatology, diagnosis and modern therapy. It is unusual in that it apparently represents the only patient who has been operated on for an aneurysm presenting into both an atrium and a ventricle. However, this combined extension into two chambers has been reported at autopsy [4].

SUMMARY

Aneurysms of the sinuses of Valsalva may communicate with a cardiac chamber, producing an aorticocardiac fistula, which is usually fatal within a few months. All ages may be affected and there is evidence that the aneurysm is probably congenital.

The disease is easily diagnosed if one is aware of its clinical features. Surgical repair is believed to be curative.

Acknowledgments: We wish to express our appreciation to the following persons for diagnostic and therapeutic contributions: Case I, Drs. Felix A. Hughes and Fred Knox; Case II, Drs. Lorin Ainger and Nell Lane; and Case III, Drs. John W. Evans and James Culbertson and the resident staff.

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A Comparative Evaluation of Prosthetic and Homologous Artery Grafts Used in the Treatment of Occlusive Disease of the Superficial Femoral Artery

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THE primary purpose of this report is to present a comparative evaluation of homografts and Dacron® prostheses employed in treating superficial femoral artery segmental occlusion. Particular attention to analysis of the graft failures emphasized the fact that structural deficiency played a prominent role in producing poor results in the homograft group. Three cases of aneurysmal formation in homografts and their management will be presented in some detail to emphasize this particular complication.

CLINICAL MATERIAL

An experience with forty-one grafting procedures in a series of thirty-four consecutive patients with segmental obstruction of one or both superficial femoral arteries was reviewed. The series subtends the period 1954 through 1959. A follow-up period of one year or longer was available for each patient, the longest follow-up period being just over five years.

Homograft Group. Homologous artery grafts were used in fifteen of the forty-one procedures. These vessels were all obtained without sterile technic from patients under forty years of age. Sterilization was done with beta-propriolactone, according to the method of Trafas and colleagues [1]. The grafts were stored at −70°C. and were thawed in warm physiologic saline just prior to use. Bacterial cultures, obtained on at least two occasions before graft implantation, were negative for growth. Care was taken not to crack the homografts before warming. No gross flaws were noted in any graft at the time of operation. Anastomoses with the host vessels were of the end to side type in all fifteen procedures. Single lengths of iliofemoral homografts were employed with eleven patients. In the remaining four procedures, three segments of iliac or femoral homografts were joined end to end in three instances; with the remaining patient five segments of iliac homografts were used to bypass a long segmental defect of the host's superficial femoral artery.

Dacron Prostheses. Dacron prostheses were employed in twenty-six procedures. With the first seven patients in this group, previously reported [2], a noncrimped, seamed tube of woven Dacron cloth was used, employing end to end anastomoses with the host vessel. With the remaining nineteen patients, operated upon in 1958 and 1959, the prostheses were of the crimped, knitted Dacron type described by DeBakey and colleagues [3]. In this latter group, end to side technic was employed utilizing the grafts as a femoral bypass.

RESULTS

Results were analyzed in the light of immediate or late failure. Immediate failure was defined as occurring within one month or less following insertion of the graft, and late failure as occurring any time after one month postoperative. In two-thirds of those cases showing immediate failure, thrombosis of the graft occurred while the patient was still in the hospital.

TABLE I
GRAFTING PROCEDURES
SUPERFICIAL FEMORAL ARTERY
St. Luke's Hospital, 1954–1960*

Number	Failure			Success
	Early	Late	Total	Total
Homografts..... 15	2	5	7 (47%)	8 (53%)
Prosthetic grafts. 26	8	4	12 (46%)	14 (54%)
Total..... 41	10	9	19 (46%)	22 (54%)

* A one to five year follow-up.

TABLE II
CAUSES OF FAILURE OF FEMORAL ARTERY GRAFTS
St. Luke's Hospital, 1954–1960*

Cause of Failure	Homograft	Dacron Prosthesis
Technic.....	1	5
Poor selection of patient.....	2	7
Structural defect in graft.....	4	0
Aneurysmal formation.. 3		
Rupture..... 1		
Total.....	7	12

* A one to five year follow-up.

As can be noted from Table I, little difference in the over-all failure rate can be distinguished between the two graft types. The increased incidence of immediate failures in the prosthetic group is probably accounted for by our early experience with the woven Dacron, which did not lend itself well to accurate anastomoses with the host vessels. Five of the seven patients in this particular category had early thrombosis of the graft. It is of interest to note, however, that Key and colleagues [4] have recorded a similar finding of a higher percentage of early failures in prosthetic grafts when compared with homografts, particularly when used in treating femoral vessel obstruction.

At the present writing, twenty-two of the forty-one procedures (54 per cent) can be classified as successful based on the patients' subjective improvement, with restoration and maintenance of one or more distal pulses in the grafted limb.

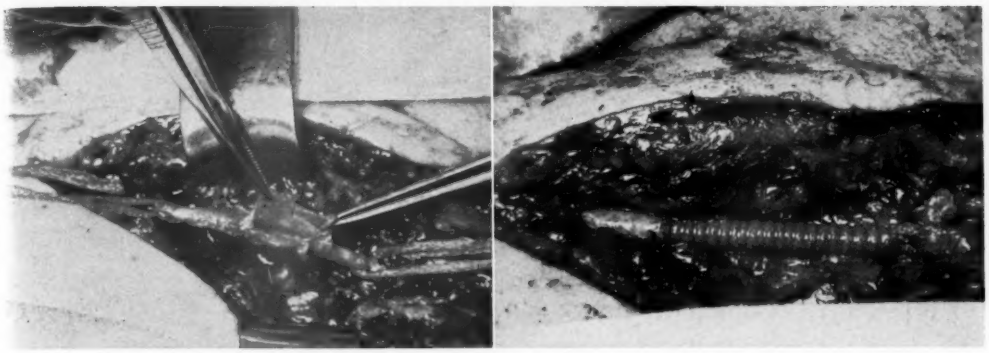
Analysis of the causes of failure in this series is presented in Table II. It is pertinent to document that of the seven clinical failures recorded in the homograft group, four were directly attributable to structural deficiency in the graft. In the prosthetic grafts there was no instance of failure due to a flaw or structural change of the graft *per se*.

It is also of interest, as can be noted in Table II, that of the four homografts showing structural deformity, aneurysmal formation occurred in three instances and graft rupture was noted in the remaining patient. The management of the three patients with homograft aneurysms presented several interesting aspects which seemed significant enough to justify outlining the three case histories in brief detail.

CASE REPORTS

CASE I. L. K., a sixty-seven year old male had a 29 cm. segment of the left femoral artery replaced with a woven Dacron prosthesis in July 1955 [2]. Restoration of distal pulses was obtained. The prosthesis, although functioning well, was removed in June 1956 because of tortuosity of the graft and wound sinus formation. A femoral artery homograft was inserted, using end to side anastomoses bridging the proximal superficial femoral vessel and the popliteal artery. Distal pulses were maintained. The patient was readmitted forty-five days postoperatively with a pulsating mass in the upper thigh which ruptured shortly after hospital admission. At operation a 3 by 4 cm. aneurysm, arising 6 cm. distal to the upper anastomosis, was noted in the homograft. (Fig. 1.) This segment of the homograft was excised and a woven Dacron graft inserted. The prosthesis was anastomosed end to end with the homograft segments remaining adjacent to the original anastomosis with the host vessel. (Fig 2.) This conduit functioned well for two weeks, at which time distal thrombosis occurred secondary to wound infection, resulting in a subsequent thigh amputation.

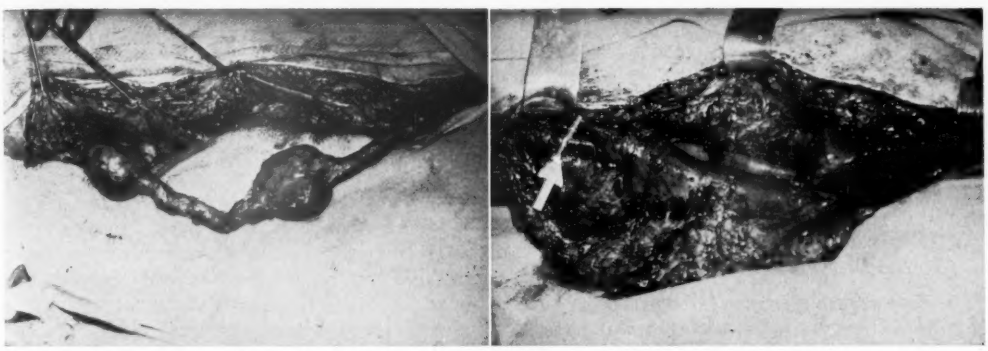
CASE II. J. A., a fifty-nine year old male had replacement of a 28 cm. segment of occluded superficial femoral artery with a woven Dacron graft in August 1955. Technically it was difficult to obtain an adequate end to end anastomosis with the proximal popliteal artery, and occlusion of the graft occurred postoperatively. In December 1957 an iliofemoral homograft, consisting of five segments of iliac homografts, was inserted as a long femoral bypass employing end to side anastomoses with restoration of distal pulses and complete relief of symptoms. Six months following this procedure the patient returned with three pulsating masses palpable along the course of the homograft in the thigh. Distal pulses were present. Exploration in



1 2

FIG. 1. Ruptured aneurysm described in Case 1 (L. K.). Proximal anastomosis of homograft to host vessel is obscured by tape.

FIG. 2. Crimped, seamless Dacron graft used to replace aneurysmal segment of homograft shown in Figure 1.



3 4

FIG. 3. Three aneurysms in an iliofemoral homograft as described in Case 2 (J. A.).

FIG. 4. Following excision of the aneurysms (Figure 3), a noncrimped, knitted dacron graft connects the proximal and distal homograft remnants. The end to end anastomosis of the Dacron graft to the proximal 3 cm. remnant of the homograft is indicated by the arrow.

May 1958 revealed three aneurysms of the homograft (Fig. 3), one of which had arisen at the site of the junction of the five grafts used to form the long homograft segment. The segment of the homograft containing the aneurysms was excised and a knitted Dacron prosthesis was sutured to the remaining 3 cm. of homograft left adjacent to the original proximal and distal end to side anastomoses. (Fig. 4.) Distal pulses have been maintained via this cloth homograft conduit to the time of this writing, two and one-half years following excision of the aneurysmal portion of the homograft.

CASE III. F. M., a fifty-six year old patient in October 1957, had a 10 cm. superficial femoral artery segmental occlusion treated by a femoral homograft bypass, using end to side technic and bridging the upper and lower thirds of the femoral artery. Distal pulses were restored and there was complete symptomatic relief. Three months later (January 1958), thrombosis occurred with immediate return of ischemic symptoms. Four months later (April 1958), following arteriographic evidence of a good "run-off," a second longer single segment of an iliofemoral homograft was inserted end to side to the common femoral artery and distal superficial femoral artery, thus bridging the entire original homograft implant. The first homograft was left untouched in the thigh tissues. Distal pulses were reestablished with complete relief of symptoms. In February 1959 the patient returned with a wound fistula and pain in the popliteal space. Exploration of the distal anastomosis revealed a 5 by 4 cm. aneurysm of the

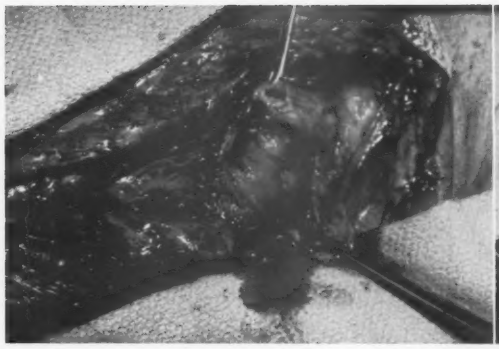


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FIG. 5. Large homograft aneurysm described in Case 3 (F. M.). Clot fills the lumen. The distal border of the aneurysm is 3 cm. proximal to the distal anastomosis of the homograft with the host vessel.

FIG. 6. Crimped, knitted Dacron graft in place after resection of aneurysmal portion of homograft described in Case 3 (F. M.). The anastomosis of the prostheses with the proximal remaining segment of homograft is indicated by the arrow.

functioning homograft, arising at a point some 3 cm. proximal to the distal anastomosis. (Fig 5.) This was resected and a crimped, Dacron knitted graft was used to replace the defect in the homograft. (Fig. 6.) Distal pulses were again reestablished. The graft was functioning well at the time of this writing, twenty-two months after excision of the aneurysm.

COMMENTS

As data on the failure of homografts accumulate, there can be little doubt that the era of the transplanted homologous artery is at an end. Structural failure, particularly in the homograft caliber used for femoral bypass, is now well documented. Szilagyi and colleagues [5] emphasized the high failure rate in homografts owing to structural graft changes. These authors stated that the relative lack of elastic tissue and the prominence of smooth muscle produced accelerated degenerative change, particularly in small caliber homografts. They further postulated that inherent structural defects leading to spontaneous thrombosis, rupture, or aneurysmal dilatation would account for inadequate function or failure in two thirds of these homografts within three years after insertion. DeWeese, Woods and Dale [6], in reviewing an experience with ninety homografts, noted eight complications directly attributable to the grafts. They reported a collected series of thirteen aneurysms in homografts, six of which had occurred in iliac or femoral grafts and seven in aortic homografts. Humphries and his group [7] described six aneurysms occurring in thirty-three grafts recovered at autopsy or secondary operation. Warren and Villavicencio [8] reported on the fate of seventeen arterial homografts remaining patent for one month or more. In their series evidence of degenerative change was apparent in eleven grafts; mural thrombosis being noted in five; early or late severe degenerative changes with or without calcification in five; and aneurysm in one homograft. Crawford and colleagues [9], in analyzing causes of failure in eighty-three cases, showed no aneurysm in Dacron or Nylon® prostheses. They did record twelve homograft failures with aneurysmal formation in four and varying degrees of graft degeneration in the remaining eight cases. The homograft aneurysms in their series were removed and prostheses employed to reestablish arterial continuity.

It is very likely that homograft aneurysms will be noted in increasing numbers. Excision of these aneurysms should be carried out with replacement of the homologous segment by a prosthesis. In the present series two of the three patients had successful removal of the aneurysmal portion of the homograft with reestablishment of distal pulses following insertion of a prosthetic graft. Distal pulses are present in these two patients thirty and twenty-two months after operation. The technic of retaining a 2 to 3 cm. segment of homograft adjacent to the original anastomoses and

bridging the defect with a Dacron prosthesis, anastomosed end to end to these segments, seemed expedient at the time of surgery and did not interfere with the already functioning anastomoses with the host vessels. The maintenance of patency up to thirty months in one patient lends credence to the belief that tensile strength is being maintained at the junction of the two nonviable materials. This technic has been mentioned by Deterling [*10*], who has used a combination of prosthetic material and autogenous vein; and by Linton [*11*], who has employed homologous arteries with segments of autogenous veins used at the end to side anastomoses with the host. Crawford and his group [*9*] also described utilizing this technic in the successful treatment of four cases of homograft aneurysm.

The over-all failure rate in this series approximates 50 per cent. This is in accord with others [*8,12*]. It can be properly emphasized that the incidence of late failures in femoral bypass grafts will undoubtedly be decreased with wider adoption of prosthetic grafts. The complications of aneurysmal formation and accelerated degenerative changes should preclude future employment of homologous arteries as femoral bypass grafts.

SUMMARY

1. A comparative evaluation of homografts versus prostheses employed in treating occlusive disease of the superficial femoral artery is presented.

2. Three cases of aneurysmal formation in iliofemoral homografts are reported with successful excision and restoration of arterial continuity in two of the three patients.

3. Structural failure as a cause of graft failure in peripherally implanted homografts is stressed. This deficiency has not been noted in Dacron prostheses.

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Experimental Appraisal of the Agents Employed as Angiocardiographic and Aortographic Contrast Media

IV. PHYSICAL AND CHEMICAL PROPERTIES

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PREVIOUS reports from this laboratory have been generally oriented toward a description and characterization of the response to injury of the test animal, when subjected to insult by the currently available angiocardiographic and aortographic contrast media [4,6,7]. The present communication deals primarily with the physical and chemical properties of these angiographic contrast media, which determine their acceptability for clinical use and which may govern the toxic potential of these contrast solutions. Sodium iodide (54.6 per cent), Hypaque® (90 per cent), Urokon® (70 per cent), Miokon® (90 per cent), Neo-Iopax® (75 per cent), Diodrast® (70 per cent) and Thorotrast® (25 per cent) comprise the angiocardiographic and aortographic contrast agents subjected to analysis.

METHOD

The composition and molecular structure of the angiographic contrast agents were compared.

Radiopacity was measured directly by the *in vitro* exposure of a fixed amount of contrast solution to radiation under standard conditions.

Viscosity was determined by measuring the rate of gravitational evacuation of contrast solution from a pipette with a capacity of 4.5 cc. Viscosity studies were performed not only on the solutions listed, but also on serial dilutions down to 50 per cent (weight/volume) concentration for each of the media tested. All viscosity determinations were performed at room temperature (23 to 24°C.).*

Osmolarity was calculated on the basis of molarity and molecular dissociation of the contrast agent. Complete dissociation of the salts of the inorganic and organic acids in aqueous solutions is likely, and such phenomenon was assumed for the purposes of deriving the relative osmolarities.

The pH was measured directly by a Beckman glass electrode pH meter model H-2. Specific gravity was determined by volumetric methods.

The physical stability as related to storage and ease of handling was also assessed. Each of the contrast solutions was placed in an open beaker and left to stand for two hours. After two hours the solutions were agitated, again left to stand, and examined periodically for the appearance of crystal formation.

RESULTS

Chemical Description. Sodium iodide is the sodium salt of hydriodic acid. It exhibits marked aqueous solubility and is 85.2 per cent iodine by weight. Aqueous sodium iodide 54.6 per cent (w/v) has an iodine content of 462 mg./cc.

Diodrast (iodopyracet) and Neo-Iopax (sodium iodomethamate) are both organic iodides derived from a pyridine nucleus; the similarities of chemical structure are illustrated in Figure 1. Diodrast (49.9 per cent iodine by weight) exists

* Hypaque (90 per cent) is a supersaturated solution which requires preheating to remain in solution after cooling to room temperature.

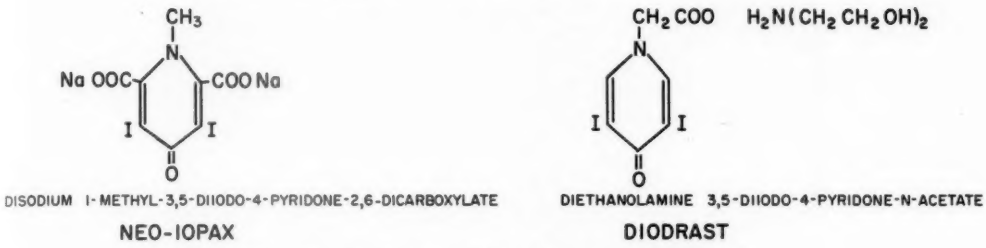

FIG. 1. The structural formulas of Neo-Iopax and Diodrast.

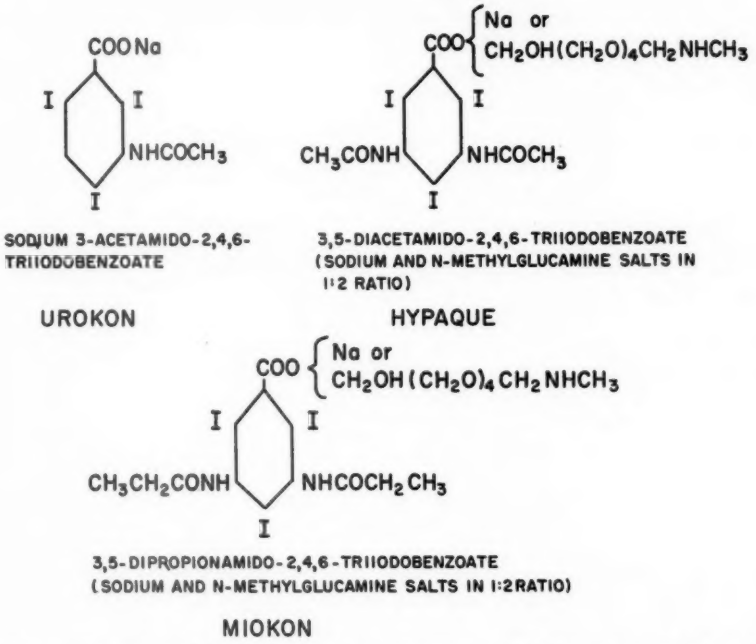

FIG. 2. The structural formulas of Urokon, Hypaque and Miokon. Note similarity of basic molecular arrangement.

only in aqueous solution and the 70 per cent solution (w/v) has an iodine content of 349 mg./cc. Neo-Iopax (51.5 per cent iodine by weight) is a white powder readily soluble in water and the 75 per cent solution (w/v) contains 386 mg./cc. of iodine.

Urokon (sodium acetrizoate), Hypaque (sodium and N-methylglucamine diatrizoate) and Miokon (sodium and N-methylglucamine diprotrizoate) are derived from a triiodobenzoic acid nucleus. The molecular differences are apparent from Figure 2, and consist principally of variations in the substituted side chains at the three and five positions in the benzene ring. Urokon is marketed as the sodium salt which is 65.8 per cent iodine by weight and a 70 per cent solution of this compound has an iodine content of 461 mg./cc. Hypaque and Miokon are prepared as both the sodium and the N-methylglucamine salts; the 90 per cent solutions used in the present studies consist of a 2:1 mixture by weight of the N-methylglucamine and sodium salts. The relative iodine content is obviously less in these latter compounds which possess both side chains and cations of greater complexity. The 90 per cent solutions of Hypaque and Miokon contain only 462 mg./cc. and 445 mg./cc. of iodine, respectively.

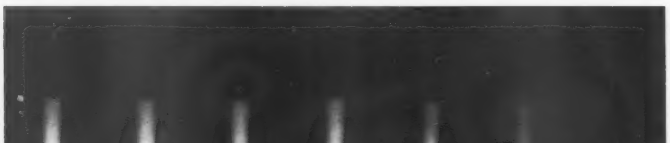

FIG. 3. Relative radiocontrast of sodium iodide 54.6 per cent (S), Hypaque 90 per cent (H), Urokon 70 per cent (U), Miokon 90 per cent (M), Neo-Iopax 75 per cent (N), Diodrast 70 per cent (D) and Thorotrast 25 per cent (T).

Thorotrast is not an iodine containing solution but a colloidal suspension of thorium dioxide (25 per cent by volume) in an aqueous solution of 25 per cent repurified tapioca-dextrin 3219 and 0.15 per cent methyl paraben. Thorium is radioactive and decays very slowly.

Radiopacity. Figure 3 demonstrates the radiographic results when the contrast solutions are arranged in the order of decreasing radiopacity from left to right. The fact that radiopacity is dependent upon iodine content can be appreciated when the contrast solutions, listed in the same order as in Figure 3, are related to their respective iodine contents as recorded in Table 1. It is to be noted that Thorotrast possesses the least radiopacity of all the solutions tested.

Viscosity. Viscosity of the contrast solutions relative to water is recorded in Table 1. As was to be expected the more concentrated solutions proved in general to be more viscid. The least viscous contrast agent was sodium iodide while Hypaque and Miokon represent the other extreme. The effect of progressive dilution of each iodine containing solution was to decrease the viscosity as depicted in Figure 4.

Specific Gravity, Osmolarity and pH. Specific gravities of the stock angiographic solutions varied from extremes of 1.32 to 1.51. (Table 1.)

All the iodide containing contrast agents are hypertonic to blood. The greatest osmolarities are possessed by sodium iodide and Neo-Iopax. (Table 1.) The osmolarity of Thorotrast could not be calculated since the number of particles per unit volume of this colloidal suspension is not known. (The average particle size is 3 to 10 mμ. as determined by electron microscopy [10].) Its osmolarity is thought to be relatively low, however, because of the extremely large particle size (and therefore minimal colligative

TABLE 1

CERTAIN PHYSICAL AND CHEMICAL PROPERTIES OF THE CONTRAST SOLUTIONS

Contrast Agent	Concentration (% w/v)	Iodine Content (mg./cc.)	Specific Gravity	Osmolarity*	Viscosity†	pH
Sodium iodide	54.6	462	1.41	23.2	0.9	8.7
Hypaque	90	462	1.49	7.8	4.5	7.6
Urokon	70	461	1.42	7.8	1.3	7.1
Miokon	90	445	1.51	7.5	4.7	7.1
Neo-Iopax	75	386	1.48	14.7	1.6	7.1
Diodrast	70	349	1.34	8.6	1.5	7.2
Thorotrast	25‡	...	1.32	...	1.8	6.4

* Compared to plasma as unity.
† Compared to water as unity.
‡ Percentage by volume.

TABLE II
SOLUTION STABILITY OF THE CONTRAST AGENTS

Agent	Per cent in Solution	Preparation*	Crystallization after Agitation†
Sodium iodide.	54.6	Solution	None at 24 hr.
Hypaque.....	90	Precipitate‡	3 hr.
Urokon.....	70	Solution	None at 24 hr.
Miokon.....	90	Solution	4 hr.
Neo-Iopax.....	75	Solution	None at 24 hr.
Diodrast.....	70	Solution	3 min.
Thorotrast....	25	Colloidal suspension	None at 24 hr.

* As supplied by manufacturers.
† Agitated after remaining undisturbed for two hours in open beakers.
‡ Exists for several hours as supersaturated solution at room temperature after prior warming.

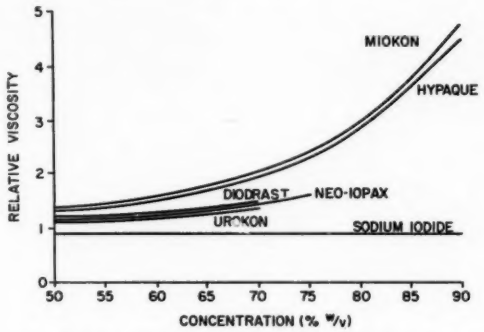

FIG. 4. Viscosity of various concentrations of sodium iodide, Hypaque, Urokon, Miokon, Neo-Iopax and Diodrast relative to that of water as unity. Note extreme rate of rise of viscosity with increase of contrast solution concentration beyond 75 per cent (w/v).

influence) of Thorotrast as compared to the crystalloid contrast agents.

The pH of the contrast solutions varied between 6.5 and 8.7. (Table I.)

Solution Stability and Ease of Handling. All of the contrast agents can be stored under seal at room temperature for prolonged periods. The iodide solutions tend to decompose on lengthy exposure to strong light.

Of all the agents tested only Hypaque requires special preparation prior to utilization. Hypaque (90 per cent) is in part a precipitate and must be heated to exist as a solution. However, after complete dissolution by heat the solution will remain supersaturated for several hours in a closed container after cooling to room temperature. All the contrast agents examined remain in solution for at least two hours if left undisturbed in open beakers at room temperature. If, however, these solutions are then agitated and again left in open beakers, crystallization appears in certain solutions. (Table II.)

COMMENTS

There are two major considerations pertinent to the evaluation of an angiographic contrast agent. The first is the assessment of the factors which influence the efficiency and facility of the agent for producing vascular opacification when utilized in clinical situations. The other consideration is the toxic potential of the contrast agent when subjected to intravascular or intracardiac dissemination.

Efficiency and Facility for Vascular Opacification. The radio-contrast resulting from injection of a contrast agent into a blood vessel or the heart is primarily dependent upon the iodine (except for noniodine containing agents) contained within the vascular lumen at the instant the radiographic exposure is made [11]. The intravascular iodine concentration is not only dependent upon the iodine concentration of the injected contrast solution but also upon the volume of contrast agent injected, the rate of injection, the locus or site of injection, the thickness (diameter) of the lumen filled with contrast medium and the dilution to which the contrast solution is subjected as a result of its introduction into the blood stream. Except for the iodine concentration and the rate of injection the aforementioned factors are not dependent upon the physical characteristics of the contrast medium *per se*. The rate of injection can be arbitrarily chosen under certain conditions in which a high pressure injection apparatus and/or a large bore cannula can be utilized [8]. Under these circumstances the radiocontrast (iodine content) of the solution itself is the critical factor in determining its potential for production of vascular opacification.

In many clinical situations, however, the use of such a mechanical injector or large bore cannula is impractical and/or hazardous. In these instances the iodine concentration and viscosity of the contrast agent both become critical factors in the production of vascular opacification for they determine the rate at which iodine can be disseminated into the vascular tree. Since both the viscosity and the iodine content of a contrast solution increase with increasing concentration of the solution, it is not readily evident at which concentration the greatest

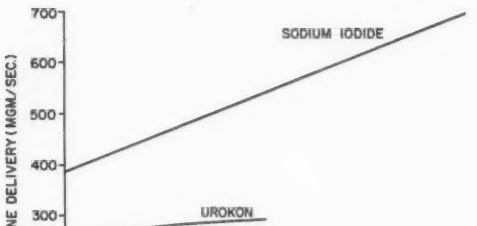

FIG. 5. Relative rate of iodine delivery possible with various concentrations of sodium iodide, Hypaque, Urokon, Miokon, Neo-Iopax and Diodrast when a standard injection technic is used.

rate of iodine dissemination is possible. Figure 5 illustrates the relative rates of possible iodine dissemination for varying concentrations of each of the iodine containing contrast media when a standard force of injection and a standard injection apparatus are utilized. The best potential for opacification is afforded by concentrated sodium iodide. Urokon, in a 70 per cent solution, possesses a better potential for vascular opacification than any other contrast medium containing organic iodide. It is interesting that with the defined injection technic (exclusion of high pressure injection apparatus and large bore cannula), the greatest rate of potential iodine delivery for the more viscid contrast media (Hypaque and Miokon) is possible with solutions of approximately 60 per cent concentration. In the case of Hypaque, the 50 per cent (w/v) solution of the sodium salt has approximately the same viscosity as a 50 per cent (w/v) solution of a 2:1 mixture of the methylglucamine and sodium salt. However, because of the relatively greater iodine content of sodium diatrizoate, the theoretic delivery rate of iodine utilizing 50 per cent sodium diatrizoate is slightly greater than is possible with any dilution of the 2:1 mixture of methylglucamine and sodium diatrizoate.

The data presented in Figure 5 are based on determinations performed at room temperature. Warming of each contrast solution to body temperature decreases the viscosity somewhat, but the relative iodine delivery rates at any given temperature are probably in the same order [5].

The relative vascular opacities obtainable by uniform injection technic for the various concentrations of the iodine containing contrast media do not vary exactly as may be anticipated from Figure 5. The reduction of the intensity of a roentgen ray beam produced by a vessel filled with contrast medium is an exponential rather than a linear function of the iodine mass per unit volume of the solution [11].

Other factors such as the ease of storage and the necessity of special preparation prior to utilization are of only minor importance in determining the selection of the most ideal contrast agent.

Toxicity. Previous reports from this laboratory have been concerned primarily with evaluation of the toxicity of the angiographic contrast media [4,6,7]. Listings of the order of the potential facility for opacification and the toxicities of the contrast media are contained in Table III. Unfortunately there is generally a direct correlation between the facility for vascular opacification and toxicity. Despite their excellent radiographic properties, sodium iodide, Urokon and Neo-Iopax are so toxic that routine clinical application seems contraindicated.

Meriting special consideration in evaluation of the toxicity of Thorotrast are its colloidal character and radioactive properties. The host organism is incapable of catabolizing or excreting this particulate material and it is phagocytosed by and permanently retained in the reticuloendothelial tissues, particularly the liver and spleen, following parenteral dissemination [3,10]. After several years much of the original dose is still trapped in the liver and spleen. The radioactivity of Thorotrast retained in the body has a biologic half-life of over 400 years, and the quantity of radiation liberated from 75 cc. of 25 per cent Thorotrast equals that liberated from approximately 3 μg. of radium [3].

The prolonged retention of Thorotrast in the liver and spleen produces a fibroblastic reaction that sometimes results in fibrosis and atrophy of these organs. There is also retention to a less extent in the bone marrow, and bone atrophy, necrosis and aplastic anemia have been reported to follow the parenteral injection of Thorotrast [10]. Specific organ perfusion with Thorotrast as occurs in arteriography has likewise provoked a granulomatous response in the

tissues supplied by the arterial tree [2]. Similarly, perivascular extravasation of Thorotrast has been followed by a granulomatous or fibroblastic reaction [1,10]. Sarcoma of the liver has been reported to follow the intravenous injection of Thorotrast, but its etiologic role in these instances is uncertain [3,9,10]. The fibroblastic and possible cancerogenic roles of Thorotrast coupled with its poor potential for vascular opacification make it less than the optimal radiographic contrast medium. However, because of the blandness of Thorotrast as regards immediate toxic reactions, there are certain situations, for instance in the patient who manifests an allergy to the organic iodide contrast media, which perhaps make Thorotrast the contrast medium of choice.

From comparison of the data of Tables I and III it can be seen that there is no strict correlation of the toxicity of an organic iodide contrast medium with the iodine content, osmolarity, specific gravity or pH of the contrast agent. There is, however, a rough inverse correlation between the viscosity and toxicity of the contrast media. It is conceivable that the high viscosity affects the vascular distribution and thereby limits the accessibility of vital portions of the perfused organ to the contrast medium [5].

The chemical structure of the organic portion of the iodine containing contrast media is probably the determinant of toxicity. The exact structural basis for the mechanism of toxicity is not obvious. (Figs. 1 and 2.) It is interesting that such small differences of chemical structure, as those which exist between Hypaque and Urokon, result in a marked difference of toxicity. (Figure 2 and Table III.)

TABLE III

ORDER OF RADIOGRAPHIC AND TOXIC POTENTIALS OF THE ANGIOGRAPHIC CONTRAST MEDIA

Contrast Agent	Facility for Opacification†	Toxicity*		
		Central Nervous System	Renal	Cardiovascular
Sodium iodide	First	First	...‡	First
Hypaque	Fifth	Sixth	Sixth	Fifth
Urokon	Second	Second	First	Second
Miokon	Sixth	Fourth	Fifth	Sixth
Neo-Iopax	Third	Third	Second	Fourth
Diodrast	Fourth	Fifth	Third	Third
Thorotrast	Seventh	Seventh	Fourth	Seventh

* Based on animal tolerance studies [4,6,7].
† When manual injection and small bore needle must be used.
‡ Central nervous system toxicity was so great that no animal survived long enough to evaluate nephrotoxicity.

SUMMARY AND CONCLUSIONS

Consideration of the data of this report permits the following conclusions as regards the choice of contrast medium for performance of angiocardiography or aortography:

1. Sodium iodide (54.6 per cent), Urokon (70 per cent) and Neo-Iopax (75 per cent) possess excellent properties for the production of cardiovascular opacification, but their toxicities are so great that their usage is probably contraindicated.

2. Diodrast (70 per cent) is capable of providing good cardiovascular opacification but it is moderately toxic.

3. Miokon (90 per cent) possesses fair potential for vascular opacification but it is moderately toxic.

4. Thorotrast (25 per cent) has poor potential for cardiovascular opacification and, although the immediate toxic responses to Thorotrast are minimal, the late reactions caused by its retention for indefinite periods within the body serve to caution against its use.

5. Hypaque possesses good potential for cardiovascular opacification and minimal toxicity. A concentrated solution of Hypaque is thought to be the contrast medium of choice in situations in which a high pressure injector apparatus and/or a large bore catheter (or cannula) can be employed. Hypaque 50 to 60 per cent seems to be the contrast solution of choice in situations in which manual injection and a small bore needle (or catheter) must be used.

These conclusions are generalizations and there are specific situations for which the use of a contrast agent other than Hypaque may be indicated. However, for routine procedures Hypaque is currently the angiocardiographic and aortographic contrast medium of choice.

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Intermittent Peritoneal Lavage

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In the treatment of renal failure, the use of peritoneal dialysis has been overshadowed by the highly publicized performance of the mechanical artificial kidney. Although less efficient than the artificial kidney, as measured by the work/time concept, intermittent peritoneal lavage has proved to be a simple, effective means of artificial dialysis and can be performed with a minimum of equipment and personnel [*1*].

The use of the peritoneum as a dialyzing membrane was introduced by Putnam [*2*] in 1923, and in the same year Ganter [*3*] first utilized peritoneal dialysis as a temporary substitute for human renal function. Since that time, several research and clinical investigators have employed the procedure with various modifications [*4–12*]; the principal refinement has been the change from a continuous to an intermittent flow [*4,10*]. Despite its success, the method apparently has never been widely accepted as a standard therapeutic procedure.

The present report concerns our experience for the past four years with intermittent peritoneal lavage at the Veterans Administration Medical Teaching Group Hospital, Memphis, Tennessee.

INDICATIONS FOR PERITONEAL LAVAGE

The indications for lavage are essentially the same as those for the artificial kidney [*4,13,14*]; briefly, they are hyperpotassemia [*4*], uremia [*4,13,15,16*], overhydration [*9,17*], chronic renal disease [*1,18*], severe electrolyte abnormalities [*1*] and selected drug poisoning [*1,19–22*]. Clinically and experimentally, peritoneal lavage also has offered temporary benefit in cases of hepatic coma and jaundice [*1*].

TECHNIC

As described by Grollman and others [*1,4*], we have employed abdominal paracentesis with a gallbladder trocar or other suitable instrument through which a lavage catheter is introduced into the pelvic peritoneal cavity. This catheter is a semirigid plastic tube similar to a Levin tube with multiple small perforations on one end. The solution is allowed to run by gravity rapidly into the abdomen where it remains for a variable period, and then by lowering the original container to the floor, the solution is recovered.

The balanced solution, recommended by Grollman [*4*], is composed of ordinary hospital fluids and pharmaceutical ingredients. Recently, several laboratories have commercially prepared and marketed fluids and a disposable lavage apparatus which further facilitate this simple maneuver. The use of these commercial preparations obviates the time-consuming procedure of mixing solutions but, more important, it lessens the chance of introducing infection and peritonitis. Maxwell and others [*1*] employed these dialyzing solutions in seventy-six patients with no evidence of peritonitis. These commercial preparations are similar in composition, and the electrolytes and approximate values are shown in Table 1.

These solutions can be obtained in two concentrations of dextrose. Dextrose (1.5 per cent) is the usual type of solution employed; however, when it is desirable to remove edematous fluid, a hypertonic solution of 7 per cent dextrose is recommended. In cases in which hyperkalemia is not a problem, potassium may be added to the lavage fluid.

Heparin added to the lavage solution apparently impedes formation of fibrin and adhesions and prevents blockage and obstruction of both the lavage and the intestine [*5,23*].

The addition of aqueous penicillin or other

TABLE I
ELECTROLYTES AND THEIR APPROXIMATE VALUES

Electrolytes	Approximate Values (mEq./L.)
Sodium (Na^+)	140
Chloride (Cl^-)	102
Calcium (Ca^{++})	4
Magnesium (Mg^{++})	1.5
Bicarbonate (by conversion of lactate)	45

TABLE II
ASSOCIATED SERIOUS MULTIPLE INJURIES AND DISEASE STATES

Diagnosis	No. of Patients
Serious multiple injuries	6
Renal sulfa precipitation	1
Blood transfusion reaction	1
Total	8

suitable antibiotics to the lavage solution reduces the chance of infection.

In our series the procedure was employed experimentally in terminal cases of chronic renal disease to determine optimal time intervals and fluid volumes. The method of peritoneal lavage can be varied to suit the individual need, but generally we have been guided by the following basic principles:

1. Baseline serum electrolytes should be determined prior to and at the termination of the lavage. Determinations of blood urea nitrogen and electrolyte composition of the returning lavage solution are helpful and have been found to parallel closely blood determination of the patient.

2. A total of 2,000 cc. of lavage solution is allowed to flow freely into the peritoneal cavity of the average adult. This period usually requires thirty minutes. The amount of solution may be reduced if the patient becomes uncomfortable or if shortness of breath occurs.

3. The solution is allowed to remain in the abdomen for approximately one hour. The maximum ionic exchange takes place early and gradually levels off [2]. The fluid is then allowed to drain off as rapidly as possible, usually requiring thirty minutes.

4. Strict accounting of fluid intake and output is recorded both as to lavage and other body fluids.

5. The patient should be weighed daily.

RESULTS

Clinical results are difficult to evaluate and compare because each case differs in some way from the others. The patients treated with intermittent peritoneal lavage at this hospital during the past four years can be divided into four groups.

Group I includes eight patients who were considered to be in acute and reversible renal failure, but most of them had associated multiple serious injuries and disease states. (Table II.) There were two survivors, but in the patients that died the procedure was also believed to be mechanically and chemically successful.

Hyperpotassemia, uremia and electrolyte abnormalities were present in all patients. The average duration of lavage was 5.5 days, and the average exchange volume of solution was 16,000 cc. per twenty-four hour period. During the first twenty-four hours of lavage, the decrease in blood urea nitrogen averaged 56 mg. per cent, and in potassium ion the average decrease was 1.6 mEq./L.

CASE REPORTS

CASE 1. A. L. was a forty-nine year-old white man with a diagnosis of lower nephron syndrome, who was transferred from another hospital where seven days previously he had undergone surgery for Leriche's disease of the aorta with excision and replacement with a nylon prosthesis [24]. Since the third postoperative day, urinary output had gradually diminished, and on the fifth postoperative day serum potassium had risen to 6.5 mEq./L. Exchange resin, although poorly tolerated, successfully lowered the potassium to 4.2 mEq./L. Upon admission to this hospital, the patient was suspected to have overhydration because of edema and weight gain. Total fluid intake since surgery had been 16,000 cc. with a seven day output of 1,555 cc. and a calculated retention of 6,000 cc. of fluid. Intermittent peritoneal lavage was instituted because of overhydration and a high level of blood urea nitrogen. A lavage of hypertonic glucose (7.9 per cent) solution was employed and two days after beginning lavage, 6,000 cc. of fluid was removed. Lavage was continued for seven days and the changes noted in blood chemistries are shown in Table III. The urine output gradually returned to normal volume.

One year later, the patient was readmitted for hypertension due to stenosis of the left renal

TABLE III
CHANGES IN BLOOD CHEMISTRY IN CASE I

Constituent	Before Lavage (mEq./L.)	Forty-Eight Hr. after Lavage (mEq./L.)
Blood Urea Nitrogen	154 mg.%	87 mg.%
CO_2 combining power	18	27
Cl^-	80	86
Na^+	110	133
K^+	4.9	4.6

artery which was relieved by splenorenal artery anastomosis.

Comment: Until recently, the peritoneal cavity in the immediate postoperative period had been regarded as a contraindication to peritoneal lavage [*1,17*]. This is one of three patients who were lavaged during the immediate postoperative period in this Institution and in whom no adverse effect was demonstrated.

Group II contains fifteen patients with chronic progressive renal disease and renal failure. (Table IV.)

Although the ultimate poor prognosis in this group was clearly known before lavage, excellent palliation was achieved in most instances. Also, the medical staff gains experience and facility which is necessary for the correct handling of acute reversible cases. The efficacy of peritoneal lavage has been dramatically impressed upon all observers in these chronic renal cases. Often a patient who is uremic, comatose and covered with frost becomes transformed into a fairly alert person within a matter of hours.

CASE II. J. S., a forty-nine year-old white man, for two years had been treated for "Bright's

TABLE V
CHANGES IN BLOOD CHEMISTRY IN CASE II

Constituent	Day of Lavage (mEq./L.)	Three Days after Beginning Lavage (mEq./L.)
Blood Urea Nitrogen	174 mg.%	102 mg.%
CO_2	4.6	22
Cl^-	96	90
Na^+	130	136
K^+	7.4	6

TABLE IV
CHRONIC PROGRESSIVE RENAL DISEASE AND RENAL FAILURE

Diagnosis	No. of Cases
Chronic glomerulonephritis	3
Arteriolar nephrosclerosis	7
Chronic pyelonephritis	3
Amyloidosis (secondary)	2
Total	15

Disease." This was manifested by severe progressive anemia, albuminuria, hematuria, hypertension and attacks of congestive failure. On admission he complained of shortness of breath, generalized muscular cramps, headaches, nausea and vomiting.

Physical examination revealed periorbital and pedal edema and a blood pressure of 124/80 mm. Hg. Indistinct disk margins were seen on funduscopic examination. The neck veins were full and the skin contained many small generalized pustules. An apical grade 2 systolic murmur was present.

White blood cell count was 13,400 per cu. mm. with 85 per cent neutrophils, and hemoglobin was 10 gm. per cent. Urinalysis revealed a specific gravity of 1.008, a 4 plus reaction for albumin, and many white and red blood cells per high power field on microscopic examination. Carbon dioxide was 8 mEq./L., blood urea nitrogen was 98 mg. per cent and chloride was 114 mEq./L.

A few days after admission, uremic frost with a pericardial friction rub developed and the patient became very restless and irrational. On January 25, 1960, serum potassium rose to 8 mEq./L. and an electrocardiogram showed evidence of cardiac irritability. The urinary output for the previous twenty-four hours had been only 215 cc. Peritoneal lavage was begun and the changes noted in blood chemistries are shown in Table V.

At the end of the lavage period the urinary output had returned to 680 cc. per twenty-four hours and the patient was alert and oriented.

Comment: This patient required three additional peritoneal lavages but died eight months and five days following his initial treatment. After each lavage, the patient became alert, oriented and able to return home for short intervals. This case demonstrates the possibility of sustaining life for prolonged periods of time in patients with chronic renal failure.

Group III includes seven patients with lethal injuries, malignant disease and/or moribund conditions that were associated with renal failure. All died from the primary disease. Lavage

was instituted only a short time before death, but renal function was irreversible.

Group IV includes one case of drug poisoning.

CASE III. C. L., an elderly white man, is but one of many patients admitted for chronic bronchitis, bronchiectasis and chronic alcoholism. On admission he was confused, delirious, lethargic and markedly dehydrated. Because of the peculiar confabulation and hallucination, bromide poisoning was suspected and verified by a high level of blood bromide (193 mg. per cent) [25]. Intravenous normal saline solution and peritoneal lavage were administered and continued for twelve hours, but were abandoned because of sudden onset of chills and fever. Six liters of lavage solution was introduced and the bromide level on the following day dropped to 105 mg. per cent. The patient became alert and cooperative. Examination of the lavage fluid yielded a total of 15 gm. of bromide salt. Saline replacement was continued, diuretics administered, and a gradual reduction in the bromide level was fortunately observed followed by prompt recovery.

Comment: The presence of chills and fever during lavage required discontinuance of the procedure. Blood culture was negative and the cause of the reaction has not been determined. No other reactions of this nature have occurred in our series and it is doubted that the lavage administration was responsible.

COMPLICATIONS

The proper placement of the lavage tube is extremely important. This was emphasized by technical errors which were responsible for laceration of the liver in one patient, and in another a large volume of fluid was introduced into the abdominal wall.

Delayed or inadequate return of fluid may be due to obstruction of the tube by fibrin, particles of fat or adhesions with loculation of fluid. Elevation of the patient's head or changes in body position often invoke a free flow of fluid. Occasionally, the tube must be reinserted or replaced. The instillation of a small amount of Pontocaine® or Metycaine® often provides relief when abdominal pain appears.

Bloody return fluid is often noticed in the uremic patient, but our experience indicates that this bleeding tendency lessens as the blood urea nitrogen lowers during the progression of the lavage. Often the bleeding is due to the trauma of paracentesis but this usually subsides [26].

Sometimes prolonged lavage induces paralytic ileus which usually responds to continuous gastric suction.

COMMENTS

Normal or near normal serum electrolyte levels were obtained in all patients, but the blood urea nitrogen remained refractory at levels which were moderately above normal. With peritoneal lavage, it is possible to hydrate or dehydrate a patient; therefore, it is mandatory that fluid intake and output be carefully monitored. Since the lavage fluid contains essentially balanced electrolytic values to which body fluids establish equilibrium, there is little danger of abnormal electrolytic levels in patients being lavaged.

The patients frequently die from varied disorders and primary diseases although the lavage has accomplished its mission of correcting the abnormalities of the patient's blood. Aspiration pneumonia and severe trauma are distressing examples of these disorders.

The principal contraindications to the use of peritoneal lavage have been extensive abdominal adhesions and diffuse generalized peritonitis, although patients with peritonitis have been treated effectively by peritoneal irrigation [27].

SUMMARY

Intermittent peritoneal lavage is a simple and effective method of accomplishing artificial renal dialysis. It is readily available to any physician with hospital and laboratory facilities and can be a life-saving procedure. Indications, contraindications, technic and results are presented and discussed.

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Extradural Hemorrhage in the Posterior Fossa

DIAGNOSIS AND TREATMENT WITH A REPORT OF TWO SURGICALLY TREATED PATIENTS

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THE classic extradural hemorrhage in the middle cranial fossa from a fracture in the temporal (squamous) bone, with a tear in the middle meningeal artery, is well known to all surgeons who deal with head trauma. However, the lesion of that type which occurs in the *posterior fossa* is much more unusual and its syndrome is much less dramatic in its development as a rule. It is very possible that it might be missed entirely unless one is alert to the possibility.

The syndrome of a surgically important extradural hemorrhage in the posterior fossa is that of a developing deep stupor with marked flaccidity and hypotonia of all the extremities, together with jerky and shallow respiration. Significantly, with these symptoms there is usually an absence of pupillary changes, hemiparesis or Jacksonian seizures and of bradycardia or rapidly rising blood pressure, such as is seen so typically in the middle meningeal hemorrhage over the temporal lobe in the middle fossa. However, there is usually (although not always) a linear fracture of the occipital bone in the posterior fossa clot cases, which may extend to the rim of the foramen magnum. Anisocoria may be present in isolated posterior fossa extradural hemorrhage. (Campbell et al. [1] made reference to six such cases in 1953.) Therefore, it is important to remember that if anisocoria is present, the patient may still have a posterior fossa extradural clot, which may also have extended above the lateral sinus. In neither of the two cases reported from our clinic in this paper, however, was anisocoria present at any time.

Two cases will be briefly reported. The first patient's record was previously published (1941) by our late chief, C. C. Coleman, and his resident at that time, J. L. Thomson [2], now of Norfolk, Virginia. This was the first reported case in the literature with a successful outcome following surgery for this lesion (1939).

As stressed by Campbell and his associates [1] in 1953 in reporting five cases of extradural hematoma of the posterior fossa (four with successful surgical results): "The principal difficulty in arriving at the diagnosis of an unusual disorder such as this often lies in failure to consider it at all (i.e., *low index of suspicion*) rather than to differentiate it, particularly if the clinical pattern is not very common or familiar. The extradural hematoma of the posterior fossa is a pertinent example. *When its presence is suspected in time*, recovery usually follows its removal; if overlooked or surgery be too long delayed, the outcome is disastrous."

It was chiefly to emphasize the rapid alteration in cerebellar and/or medullary compression which characterizes the course of this lesion in certain patients that Campbell and his associates presented their paper in 1953.

Usually, in fact almost always, there is a demonstrable linear fracture of the occipital bone running vertically or rather vertically ending frequently in the foramen magnum itself. This fine line (as it often is) may be seen, however, only at the time of operation; i.e., the skull x-ray films may be "normal." The fracture may even be compound and depressed. The presence of such a fracture accompanied by the developing symptoms described here is highly suggestive of an extradural hemorrhage in the posterior fossa. Even a soft tissue injury

of the occipital region without x-ray evidence of skull fracture, followed by signs and symptoms of cerebellar or medullary dysfunction, should cause one to suspect the existence of this lesion. One or more lucid intervals is not uncommon. A history of immediate unconsciousness following trauma is not absolutely necessary for the diagnosis of posterior fossa extradural hemorrhage. Case 1, reported later in this paper is an example. Campbell et al., in reporting five cases (1953), stated that three of their patients (like Case 1 herein reported) had no history of immediate unconsciousness.

It is well to remember that neither the surgically demonstrated presence of a supratentorial clot over a cerebral hemisphere nor the roentgenologic failure to demonstrate an occipital fracture entirely excludes the presence of an extradural hemorrhage in the posterior fossa. Sometimes the fine hairlike fracture line in the occipital bone is not seen on the x-ray films at all but is demonstrated only at the time of operation. The rarity of this clinical entity is borne out by the fact that such well known textbooks on head trauma as those of Brock [3], Gross and Ehrlich [4], Munro [5] and Davis [6] do not mention this lesion or consider it very unusual. Campbell and his group [1] encountered only three instances in a series of 970 consecutive cranial-cerebral injuries at the Albany, New York Hospital (an incidence of 0.3 per cent). We have seen it in only two verified surgical cases among several thousand patients with acute and chronic head trauma in our clinic. A single instance of chronic epidural hematoma in this anatomical location, with a ten months' latent interval, has been published by Turnbull [7]. A study of our own and other reported cases suggests that there are two distinct groups of posterior fossa extradural clots to be observed: first, those which are rapidly fatal due to *acute brain stem compression*, and second, those that pursue a more *subacute course*, characterized by progressive or intermittently developing cerebellar, bulbar-nuclear and long tract signs.

In the subacute group (the more favorable type), the mass of extradural blood expands slowly, permitting the underlying cerebellum and brain stem to accommodate themselves to it for some time. Signs and symptoms include increased intracranial pressure, alone or combined with cerebellar dysfunction, as well as medullary or bulbar-nuclear dysfunction. They may vary greatly from day to day, as in our Case 1, or even from hour to hour, but usually with eventual worsening of the clinical state. Occipital trauma, with or without demonstrable skull fracture by x-ray examination, is quite common, in fact, the rule in posterior fossa extradural clot cases. In differential diagnosis an intracerebellar hematoma may produce a similar clinical picture, as shown by McIver [8] in the instance of a thirteen year old girl, whom he reported to have had a head injury without loss of consciousness. Two days later she complained of headache and a day later she began to vomit. When she was admitted to the hospital, there were no abnormal neurological findings. A few hours later there was a sudden failure of respiration, followed within twenty minutes by cessation of cardiac function. Autopsy revealed a partially liquid clot about the size of a walnut within the substance of the left cerebellar hemisphere.

As has been stressed by several writers, intracerebellar hemorrhage may produce a practically indistinguishable clinical picture from that of extradural hemorrhage in the posterior fossa. An illustrative case of intracerebellar hemorrhage was cited by Coleman and Thomson [2] in their report of the first successful surgical removal of a posterior fossa extradural clot (1939). Their patient, a young boxer, had received a light blow on the back of his head and about twenty-four hours later became quite drowsy. He would persistently lie on his side and, when turned on his back, would vomit violently and rapidly turn to the side again. At the time of the operation Coleman removed a large acute intracerebellar hematoma and the patient made an uneventful recovery.

In addition to the surgically important extradural clot in the posterior fossa, there may be subdural bleeding from gross intradural cerebellar injury, such as laceration or marked contusion of the cortex. Case 11, herein reported, is an instance. In Lemmen and Schneider's [9] Case 1, reported in 1952, the patient had an intradural cerebellar injury in addition to an extradural hematoma in the posterior fossa. Therefore, if the clinical picture is sufficiently suggestive to warrant further exploration, it is as important to pursue a clot beneath the dura and/or within the cerebellum itself as in the usual supratentorial exploration for acute head trauma.

The *pathogenesis* of posterior fossa extradural clot is of considerable interest. Several writers

have stressed that such clots are invariably the result of tears in a venous sinus, yet in several instances in the literature the hematoma did not extend to, nor did it seem to arise from, any of the venous (dural) sinuses.

It is wise to resort occasionally to ventriculography in problem patients with acute or subacute head trauma that do not improve (especially in their state of consciousness) after the usual superior temporal and/or frontal burr openings have or have not disclosed a subdural or extradural hematoma. A ventriculogram may show internal hydrocephalus, suggesting a posterior fossa clot that should be dealt with surgically without delay, and usually with satisfactory results.

Spinal puncture is not helpful, preoperatively, in these instances and may be distinctly unwise. It was not used in either of the cases reported here, both having a successful surgical outcome. The withdrawal of spinal fluid below such a developing lesion in the posterior fossa, as in any cerebellar mass lesion, may lead to foraminal herniation of the cerebellar tonsils with medullary compression, sudden respiratory failure and immediate or somewhat delayed death. Furthermore, the absence or presence of gross blood in the spinal fluid would not be of particular help in the precise differential diagnosis of this lesion. Our experience and judgment would advise against spinal puncture in the study of suspected posterior fossa hemorrhage.

Surgically, the evacuation of posterior fossa clots is even simpler than the more common middle meningeal extradural clot over the cerebral convexities as there is usually no sharply bleeding arterial vessel to deal with in the former type of case. It suffices to remove as much occipital bone caudad to the lateral sinuses as necessary to evacuate the clot and control the source of the bleeding with a muscle implant or Gelfoam® in the extradural space.

CASE REPORTS

Case 1. A Negro boy, nine years of age, was admitted to St. Philip's Hospital (Medical College of Virginia Hospitals). Two days previously he had fallen from a moving truck, striking his head, but was not rendered unconscious. Brought to the emergency room shortly thereafter, he was alert and cooperative and the only sign of injury was a small hematoma of the scalp in the left occipital region. The neurological examination was entirely negative and he was allowed to go home. He returned in twenty-four hours because of headache and moderate drowsiness and he had vomited on two occasions. Again the neurological examination was essentially negative. The child was taken home again, then brought to the hospital a third time the following night. He was at that time moderately drowsy and restless, complained of headache and had vomited again on several occasions. There were no other neurological signs. He was admitted to the hospital for observation. Shortly thereafter, he became very drowsy and moved his extremities only after painful stimulation. X-ray examination of the skull showed a long linear fracture line extending from the lambdoidal suture downward into the foramen magnum to the midline. The child cried out when attempts were made to flex the neck. The pupils were equal in size, moderately dilated but reacted to strong light. There was no nystagmus. All cranial nerves were functioning normally and the optic discs were well outlined. He moved all his extremities well, but there was generalized hypotonia. The deep tendon reflexes were entirely absent (see postoperative status mentioned later). There was no Babinski sign and the blood Wassermann reaction was positive. The child invariably lay on his left side. There was a linear fracture of the occipital bone, so it seemed most likely that there was a hematoma in the posterior fossa causing cerebellar compression and obstructive hydrocephalus.

At the time of the operation (Thomson) bilateral anterior parietal burr openings were first made to rule out a possible clot over a cerebral hemisphere. No such clot was disclosed. Thirty cc. of clear fluid was obtained from the left lateral ventricle. This moderate hydrocephalus gave apparent proof that obstruction was present in the posterior fossa. The patient was turned on his abdomen and a burr hole was made over the center of the right cerebellar hemisphere. Immediately, about 10 cc. of old dark blood escaped under pressure from the extradural space. An organized blood clot was readily visible beneath this, necessitating an extension of the scalp incision and removal of the bone over the right and left cerebellar fossae in order to expose the hematoma completely. The posterior fossa clot was at least 3 cm. thick near the midline and had compressed the midline structures of the right cerebellar hemisphere considerably more than the left. It had extended on the right lateralward to the sigmoid sinus. The dura enclosing the lateral sinus was stripped from the bone near the torcular, while on the left the edge of the clot was near the sigmoid sinus. As a small portion of the clot was being aspirated away from the torcular, there was profuse venous bleeding. It was therefore concluded that the torcular herophili had been torn when the skull was fractured and

that the lacerated venous sinus was the source of the extradural hemorrhage. The bleeding point was occluded with muscle. Respiration improved immediately after removal of the clot. The scalp wound was closed with interrupted silk sutures with one rubber tissue drain placed in the extradural space. The dura was not opened. The patient reacted promptly from the anesthesia and four hours later he could talk coherently but was still moderately drowsy. Improvement continued steadily throughout the next few days and recovery was uneventful. He was discharged sixteen days after admission. At that time he had no ataxia. When seen one year postoperatively, the child had no complaint and the neurological examination was negative; in particular, the deep tendon reflexes in all four extremities were then easily obtained (see preoperative status previously mentioned) and were equal bilaterally. There was no evidence of residual neurological impairment.

Comments: The relatively slow onset of symptoms in this patient (more than sixty hours having elapsed following trauma before marked drowsiness appeared) was due probably to the slowly forming extradural clot in the posterior fossa producing obstruction of the ventricular system, rather than to the direct pressure of the clot on the cerebellum and brain stem. A hematoma from venous sinus origin forms slowly because the venous pressure within the dural sinus is only about 4 to 6 mm. Hg. Since there are no large arterial vessels on the dural surface of the posterior fossa, it is safe to assume that all, or at least most, of the surgical clots in this region would be of venous origin. Therefore, a rather long latent period, possibly even a number of days or weeks, may intervene between the time of injury and the onset of symptoms indicating the presence of a posterior fossa clot. It should again be emphasized that the injury in this patient did not produce unconsciousness at the time of trauma. Such a negative history often tends to make the resident and intern staff underestimate the importance of certain head trauma cases when first seen in busy hospital emergency rooms. As mentioned previously, other occurrences of the lesion under discussion have been reported in the literature in which there was *no initial loss of consciousness and even no skull fracture demonstrable on x-ray examination.*

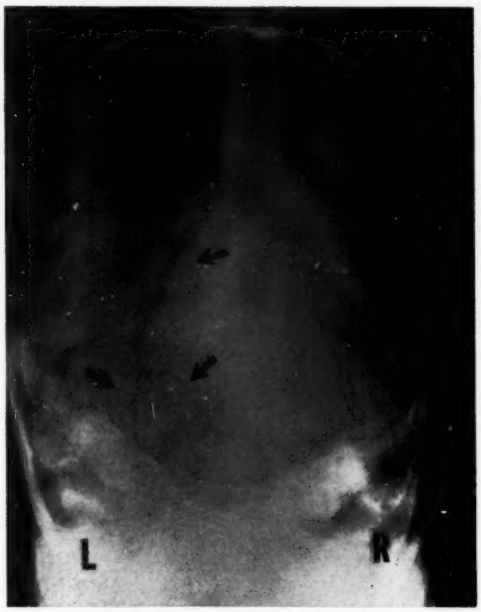

FIG. 1. (Case II) Note the almost vertical linear fracture of the left occipital bone (arrows), which extends to the region of the foramen magnum in a stellate fashion (lower end) beneath which was the extradural hematoma (see text). An anterior-posterior x-ray view of the skull.

CASE II. A white boy, two years of age, was admitted to the Medical College of Virginia Hospital on May 11, 1959 and was discharged on May 25, 1959. He had fallen out of the back seat of a car which was traveling at a moderate rate of speed. He was rendered unconscious immediately but was awake on arrival in the emergency room, although quite drowsy. He could, however, be aroused readily but was somewhat irritable. X-ray films disclosed a linear fracture of the occipital bone extending to the foramen magnum, which was somewhat fragmented at its point of termination. (Fig. 1.) Marked bleeding from the nose and mouth was thought to be due possibly to an injury in the left mastoid area involving the sigmoid sinus, with bleeding down the Eustachian tube into the pharynx.

The following morning the child was much more alert, recognized his mother and played with his toys. However, about twenty-four hours after trauma, a different and alarming state developed; the patient became completely unarousable, with marked restlessness and constant motor activity. There were no true grand mal seizures, either generalized or Jacksonian. No inequality of the pupils was observed at any time to suggest a cerebral hematoma, either extra or subdural. Recalling the *long linear fracture in the occipital bone,* we suspected the possibility of an extradural hematoma in the posterior fossa and an operation was performed

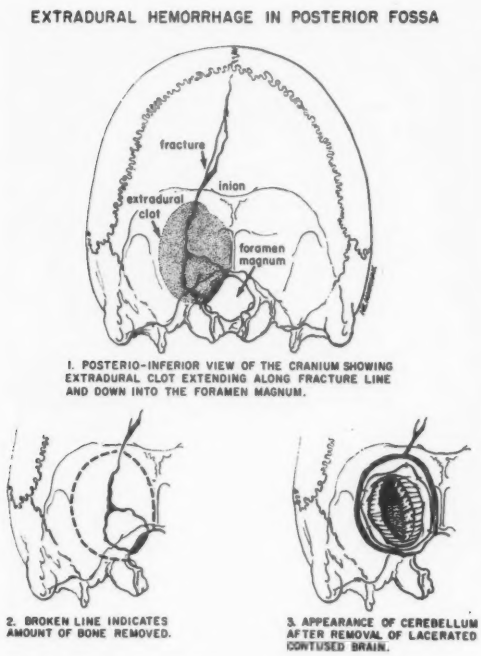
EXTRADURAL HEMORRHAGE IN POSTERIOR FOSSA
fracture
inion
extradural clot
foramen magnum
1. POSTERIO-INFERIOR VIEW OF THE CRANIUM SHOWING EXTRADURAL CLOT EXTENDING ALONG FRACTURE LINE AND DOWN INTO THE FORAMEN MAGNUM.
2. BROKEN LINE INDICATES AMOUNT OF BONE REMOVED.
3. APPEARANCE OF CEREBELLUM AFTER REMOVAL OF LACERATED CONTUSED BRAIN.

FIG. 2. (Case 11) Artist's conception of the clot found at operation. (1) Stippled area shows the extent of the hematoma in the extradural space beneath the linear and stellate fracture of the occipital bone on the left side; (2) the broken circular line indicates the amount of bone that had to be removed to enable the entire clot to be evacuated and to discover the extent of the lacerated dura (see text); (3) gives the final appearance of the cerebellum after the lateral fourth of the left hemisphere had been removed, as it had been damaged by laceration and contusion beyond hope of restoration.

shortly after the urgent complications mentioned previously developed.

With the child in the cerebellar face-down position, a linear vertical incision was made in the scalp as in the exposure of a midline cerebellar tumor. The fracture line was seen in the left occipital region, running vertically from above the inion down to the left side of the foramen magnum. It then turned medialward to approach that opening. Several loose fragments of bone as large as a fingernail were removed after separating them from the periosteum. A fair-sized extradural hematoma was found under the lower end of the linear fracture of the skull, compressing the dura over the cerebellum; it was 2 cm. thick in its thickest portion. (Fig. 2.) As the bone was rongeured away and the extradural clot aspirated by the suction apparatus, it was found that the dura also had been torn by the fracture line. After the extradural hematoma had been removed and the dura opened

FIG. 3. (Case 11) Postoperative photograph (of the simple vertical incision used to evacuate the hematoma) made one week postoperatively.

and sutured back to the surrounding muscles, it was observed that the lateral portion of the left cerebellar hemisphere was extremely contused, lacerated and even liquefied. This portion was aspirated freely with a glass suction apparatus. In all, about the lateral fourth or third of the left cerebellar hemisphere was aspirated before the contused and amorphous cerebellar tissue was removed. Fortunately, the removed tissue was lateral to the dentate nucleus, otherwise a postoperative left-sided ataxia very probably would have developed.

No undue bleeding at any time and no bleeding of any venous (dural) sinus were encountered, although the exposure was quite near the occipital sinus in the midline and the large veins that surround the cisterna magna. The dura was opened for a distance of 5 by 4 cm. overlaying the lower portion of the left cerebellar hemisphere and was left sutured to the surrounding muscles, thus carrying out a so-called unilateral cerebellar decompression precisely as performed in a hemicerebellar attack on a cystic neoplasm. Closure was made without drainage and the child was returned to his room in good condition. He regained consciousness promptly, and within six hours, postoperatively, he was entirely awake and recognized his family. His progress was quite satis-

factory; his operative wound healed well *per primam.* (Fig. 3.) On July 3, 1959, almost two months after the operation, he was in excellent condition, having no ataxia and being alert and playful. There appeared to be no neurological deficit at that time or at another follow-up examination six months after the operation. (Fig. 4.)

Comments: The somewhat delayed and alarming clinical picture in Case II was perhaps due to the combination of the accumulating extradural hematoma over the cerebellum and the edema of the underlying contused and lacerated cerebellar hemisphere, with resultant transmitted pressure to the medulla and other portions of the brain stem. Thus unconsciousness was produced, and even deep coma, with *marked flaccidity of all the extremities* together with the peculiar agitation and restlessness of the patient (i.e., constant motor activity) and shallow jerky respiration.

FIG. 4. (Case II) Photograph of the patient six months after removal of the posterior fossa extradural hemorrhage showing his normal appearance. There was no neurological deficit at this time, nor has any appeared since that date to the writer's knowledge.

COMMENTS

Case II illustrates also that alert clinical observation of the patient with frequent neurological examinations by the house and attending staff and the nursing staff is very important in the management of all head trauma cases. This is necessary in order to observe the sometimes rapid progression of bilateral hypotonia and hyporeflexia, which may quickly become evident in these particular patients as drowsiness increases. Case I illustrates how easily this syndrome may be overlooked in a cursory examination in the emergency room and dismissed as of little clinical importance if the patient is alert and *without a history of initial unconsciousness:* Hence no skull films were made at first. Stress should be laid also upon the importance of admitting to the hospital all patients with head trauma for at least twenty-four hours' observation if they have been unconscious, although this rule was not applicable in Case I. This has been an invariable rule in our clinic for several decades to insure that no complications develop or to enable us to deal promptly with such complications should they occur. This admission rule applies in our clinic not only when x-ray films disclose a fracture of the skull but for all patients with head trauma seen within a few hours after injury, if there is a history of initial or delayed unconsciousness. Case I also illustrates the now well-known fact that *there may be extensive skull fracture without initial loss of consciousness at all.* Also as already mentioned, a *patient may develop this lesion without skull fracture or even without initial loss of consciousness.*

The *development of cerebellar signs,* with this particular lesion, in posttraumatic cases is most important. Although this pathological entity is quite rare even in large surgical clinics dealing with many head trauma cases (seen in only 0.1 to 0.3 per cent of all head injuries), it should always be considered in an increasingly drowsy patient, who has evidence of cerebellar compression and a linear fracture of the occipital bone, usually with definite soft tissue injury in the same area. Burr openings over the cerebellum may result in the lesion being easily discovered and removed, with recovery of the patient, if the operation is performed before respiration and other vital functions have been impaired too seriously or for too long a time.

Coleman, approximately twenty years ago, gave these criteria for the recognition of an extradural hematoma in the posterior fossa, which have been supplemented to some extent by the present writer: A history is present of a blow on the back of the head, usually but not always severe enough to produce a linear fracture of the posterior fossa of the skull, which may or may not cause initial unconsciousness,

i.e., concussion. Furthermore, the fracture may not be clearly demonstrable even on skull x-ray films, but there should be edema or swelling or contusion or even laceration of the scalp in the occipital region; stellate or even depressed skull fractures have been reported over such extradural clots. Then a headache of increasing severity develops which is usually accompanied by nausea and vomiting. There are, however, often curious *variations and fluctuations* in the state of consciousness and the alertness of the patient, for the first day or two, or even longer. Drowsiness and restlessness will continue, however, and progress until the patient lapses into deep unconsciousness. During the drowsy state several important localizing signs may be noted. The patient often seems to prefer to lie on one side, usually the side of the lesion, and will promptly return to that side when placed on his back. This last-mentioned fact is also true of many other cerebellar lesions, including abscess or unilateral tumor, as all surgical neurologists know. Nuchal rigidity may develop, nystagmus may or may not be present, and deep tendon reflexes are suppressed rapidly or even completely disappear so that a *peculiar bilateral flail-like flaccidity or hypotonia and areflexia of all the extremities usually develops*. This is highly characteristic of this lesion, along with deep stupor and shallow, jerky respiration, together with the skull x-ray findings. The pupils usually remain equal in size but there may be anisocoria or even a complete third nerve palsy. As unconsciousness deepens, the pulse and respiration become irregular and death will occur unless there is prompt surgical intervention with removal of the extradural posterior fossa clot.

SUMMARY AND CONCLUSIONS

Extradural hematoma of the posterior fossa is fatal unless it is removed before bulbar compression becomes extreme. While the diagnosis can be based on clinical and x-ray findings alone, as shown here, it may be necessary (where there is a delayed clinical picture) to resort to ventriculography to demonstrate a posterior fossa mass lesion, via internal hydrocephalus. Whether or not a supratentorial extradural hematoma overlying the frontal or temporal region in the individual patient has been found previously, the possible concomitant existence of one of the rarer extradural hematomas of the posterior fossa must be borne in mind. This possibility must be considered if stupor continues and there are additional signs of cerebellar or medullary compression, particularly if associated with (1) soft tissue trauma and/or skull fracture in the occipital region in or approaching the region of the foramen magnum, and (2) hypotonia and areflexia of the extremities on one or both sides.

Above all, it is the *high index of suspicion* which suggests that this lesion may be present, with the previously mentioned symptoms and signs, that makes for *surgical success* with the individual patient, provided that a prompt operation for removal of the clot is carried out when the presence of the lesion first appears likely.

ADDENDUM

Since the writing of this paper, a report has been published [*10*] of an extradural hematoma of the posterior fossa with an associated space-occupying collection of fluid in the subdural and/or subarachnoid space just beneath the extradural hematoma. In this case in which the patient was an adult, an extradural hematoma in the posterior fossa of approximately *25* cc. in volume was removed and directly beneath the dura a collection of 40 cc. of fluid was evacuated. The usual telltale vertical linear fracture line into the foramen magnum was present. Apparently, this is the first recorded case in which a large surgically important extradural hematoma of the posterior fossa was associated with an even larger subjacent subdural (or subarachnoid, perhaps both) hygroma. A preoperative injection of spinal air showed very satisfactorily the extradural hematoma for the magna cisterna and basilar cisterns were definitely deflected anteriorally from their normal position shown on the lateral air film view of the skull. The patient recovered promptly following evacuation of these two pathologic collections of fluid in the posterior fossa.

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The Use of Full Thickness Grafts and Suction Following Radical Mastectomy

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IT IS difficult to obtain primary healing in many wounds following radical mastectomy if the amount of skin excised is adequate. What constitutes adequate skin excision? Haagensen says, "I try to place the skin incision at least four fingerbreadths—that is, about 7 cm.—beyond the edge of the palpable tumor" [1]. Many experienced surgeons maintain that such wide excision of skin is not necessary and feel that grafting of skin is seldom indicated. It has been my practice to keep the incision at least 5 cm. away from the palpable margin of the tumor or from the biopsy site. The skin of the entire breast has been removed in the occasional instances of extremely large tumors.

This policy of excision of skin has led to delayed healing of wounds in many cases due to skin necrosis resulting from excess tension on the flaps when primary closure is performed. Accumulation of fluid beneath the flaps has also been a problem during the early postoperative period. These complications increase the morbidity of the procedure.

When it is evident, at the close of the operation, that the skin edges cannot be approximated without excess tension, grafts have been used. Formerly, split skin grafts were utilized; however, since Slattery's article appeared in July 1956 [2], full thickness grafts have been taken from the excess skin surrounding the radical mastectomy wound. The skin is usually taken from the lower portion of the lateral flap. (Fig. 1.) This eliminates the necessity for a distant donor site which adds to the patient's discomfort during convalescence.

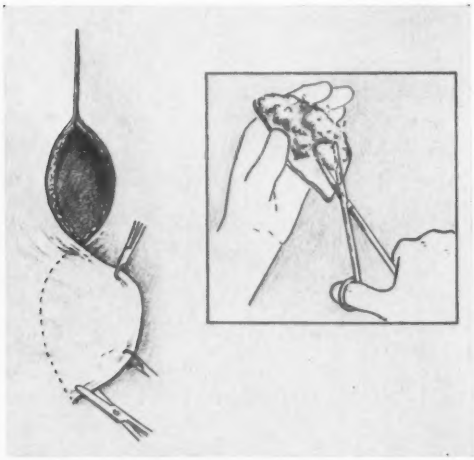

FIG. 1. Excising and preparing full thickness graft.

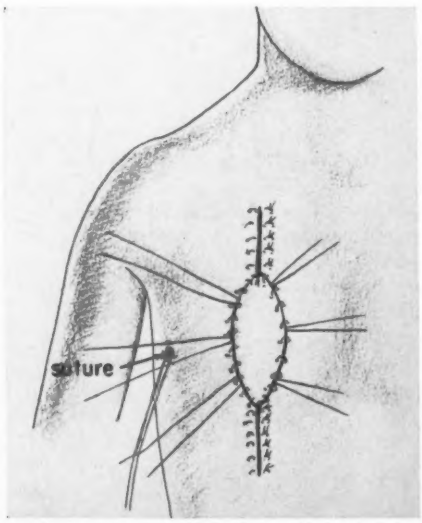

FIG. 2. Careful skin closure with graft fixation and tube in place for gentle suction.

* Address: 5101 Caroline Street, Houston 4, Texas.

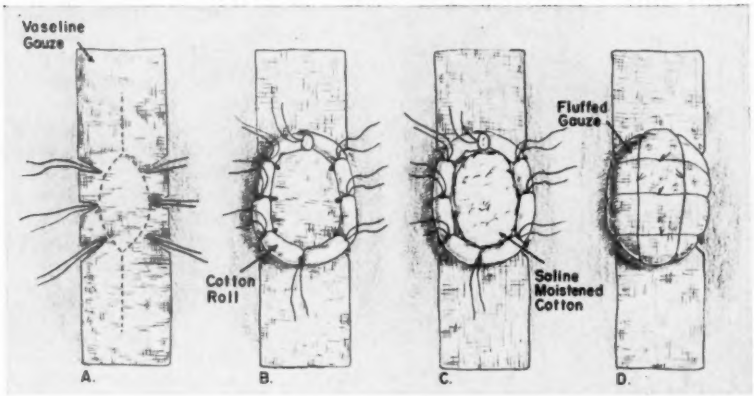

FIG. 3. Application of a stent dressing.

The use of gentle suction beneath the flap as described by Rafft [3] has been extremely helpful in the management of accumulation of fluid beneath the flaps. In his brief article, Rafft's concluding statement was, "Of course, this method will not apply when skin grafting is necessary." However, it has proved to be most helpful in the method of wound closure described.

There are several technical details which are regarded as important in good healing. These are the following: (1) The skin edges of the flaps must be carefully approximated with closely placed sutures. We use interrupted silk sutures. The graft is sutured over the defect, which is usually near the middle of the wound, with No. 3–0 silk sutures which are tied and the ends left long to be utilized for application of a stent dressing. (Fig. 2.) The edges of the graft are sutured to the skin flaps with a continuous No. 5–0 silk or Dermalon® suture, completing a water-tight closure. (2) A stab wound is made with a No. 11 blade in the lateral flap near the posterior axillary line. A size F22 or F24 urethral catheter with two or more additional holes is passed through this opening anterior to the latissimus dorsi muscle, and the tip is anchored with a plain No. 2–0 suture (one loop) approximately 1 inch away from and below the axillary vein. (3) The wound is then carefully irrigated with normal saline, using an asepto or piston-type syringe, following which gentle suction is applied to the catheter until the skin lies snugly against the thoracic wall. (4) The dressing is then applied as illustrated. (Figs. 3 and 4.) A clamp is applied to the catheter before the suction is discontinued. The patient is transported to the recovery room where the catheter is immediately attached to a Wangensteen suction apparatus or Stedman pump following which the clamp on the catheter is removed. Suction is maintained for three days, at the end of which time the tube is clamped, detached from the suction apparatus and taped to the dressing. The first postoperative dressing is done on the fifth or sixth postoperative day, at which time the catheter is removed.

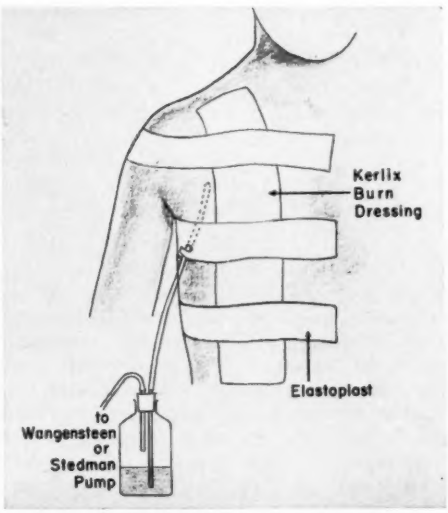

FIG. 4. Final dressing and suction tube.

FIG. 5. Postoperative photograph (Case v).

RESULTS

This method has been used in six cases. The results are as follows: (I) Case I, 70 per cent take; Case II, 90 per cent take; Case III, 70 per cent take; Case IV, 100 per cent take; Case V, 100 per cent take; and Case VI, 100 per cent take.

The smallest graft was 2 by 3 cm. The largest (Fig. 5) was 5 by 8 cm. The remaining four were intermediate in size. The "take" was 100 per cent in the last three cases. The most recent case is reported in detail.

CASE REPORT

The patient (Case VI), a fifty-three year old white woman was seen first in the office July 23, 1960. She complained of a "lump" in the right breast which had been present for three months.

Physical examination revealed an irregular firm mass occupying the upper outer quadrant of the right breast. The size of the mass was 2 by 3 cm. and there was slight skin dimpling over the center of the mass. Supraclavicular and axillary regions were negative for palpable nodes. The other breast was normal. The liver was not palpable and the remainder of the physical examination was entirely negative.

Results of laboratory examination were as follows: urinalysis was negative; complete blood cell count was normal; and Wassermann test of the blood was negative. X-ray films of the chest, lumbar spine, pelvis and hips showed the following: the chest was negative and there were osteoarthritic changes in the lumbar spine.

The diagnosis of tumor of the right breast, probably carcinoma, was made. Surgery was performed on July 27, 1960. An incision biopsy was performed since the lesion was large and regarded clinically to be carcinoma. The edges of the skin of the biopsy wound were closed snugly with a running silk suture. The closed incision was cleansed with saline sponges and sealed with collodion and Telfa.® The frozen section was reported as carcinoma. The operative area was cleansed with pHisoHex,® painted with Zephiran® and redraped for radical mastectomy. A full thickness graft and gentle suction, as described herein, were used to attain wound closure. The dimensions of the graft were 5 by 7.5 cm.

The pathologic diagnosis was as follows: carcinoma, duct cell; and regional lymph nodes, metastatic carcinoma in four nodes out of twenty-four removed.

The take of the graft was complete. X-ray therapy was given between August 10 and September 2, 1960. The photograph (Fig. 5) was taken three months after radical mastectomy.

CONCLUSION

A satisfactory and simple method of closure of radical mastectomy wounds has been reported. The method combines the use of full thickness skin grafts taken from excess skin around the wound with gentle suction beneath the snugly closed skin flaps. This method avoids the use of a separate donor site.

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The Surgical Treatment of Radiation Dermatitis Following Irradiation of Benign Diseases

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Eighty patients with radiation dermatitis, who were exposed to radiation either accidentally or for a benign disease, have been treated in the Plastic Surgical Service of the Hospital of the University of Pennsylvania. Although most of these patients were exposed to radiation many years ago, some were irradiated recently. The use of radiation for treatment of benign disease except in the hands of skilled radiotherapists may be disastrous, but some physicians still use it in poorly conceived management of certain undiagnosed or benign lesions such as neuritis, infection, acne vulgaris, eczema, plantar wart and hemangioma as well as infection and superfluous hair [1]. In other instances, accidental exposure has been followed by equally disastrous sequelae. It is our purpose to illustrate the dangers of irradiation under these circumstances and to describe the surgical treatment of the sequelae. In all of our eighty patients, the diagnosis was confirmed by pathologic examination, and complete follow-up data are available on all patients.

PATHOLOGY AND DIAGNOSIS OF RADIATION DERMATITIS

Shortly after the discovery of roentgen rays in 1895, reports of the ill effects of ionized radiation in human tissues began to appear.

In 1896, Daniel [3] described skin depilation following exposure to roentgen rays. In 1902, Codman [2] found 167 cases of accidental roentgen ray "burns" in the literature, and in 1909 Wolbach [7] in a classic paper described the pathologic histology of chronic radiation "dermatitis" and early superimposed carcinoma. In spite of this early experience, ionizing radiation has been freely used to treat benign diseases, often with severe changes in normal tissue and frequently followed by the development of cancer.

The diagnosis of injury to the skin due to radiation is not difficult when the injury is severe. Characteristically, the skin is atrophic and scarred with increased fibrosis and contractures. There is hypo- and hyperpigmentation, loss of hair, sweat and presence of sebaceous glands. There may or may not be chronic ulceration. If malignancy is present the gross characteristics may be obscured somewhat by the presence of the damage from radiation and by the numerous keratodes which may also arise in the area of chronic radiation dermatitis. A cancer may appear as a firm thickened area in the irradiated skin, or there may be ulceration associated with malignancy without any characteristic changes attributable to the cancer. At times there may be a large growth with unmistakable malignant characteristics. (Fig. 1.) The diagnosis is furthered by the fact that the edges of the lesion of the skin are often limited and correspond accurately in size to the portals of the X-ray machine.

Saunders and Montgomery [5] have formulated the following classification of injuries from radiation which is based on the extent of the injury. Criteria for injuries of the first degree are the cutaneous changes of atrophy, sclerosis, telangiectasia, pigmentation, alopecia and diminished sweat and sebaceous function.

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FIG. 1. Fibrosarcoma of the hand of E. C.

Those for injuries of the second degree include the aforementioned changes plus small ulcers or numerous keratodes. All of these plus the presence of large ulcers constitute a third degree injury.

Warren [6] has stated that the production of visible change in the skin (erythema) has been used as the biologic standard of therapeutic radiation. He states that erythema is produced in a 6 by 8 cm. field with 400 r unfiltered soft roentgen radiation.

The erythema which results from x-ray exposure will appear a few hours to a few days after the exposure and then will disappear, only to reappear ten to twenty-eight days later. This is followed by the development of some degree of permanent pigmentation. If the damage is moderately severe, acute radiation dermatitis appears in the irradiated area as the erythema first subsides. The skin becomes inflamed and edematous and undergoes desquamation. If the damage is more severe, hemorrhage accompanied by fibrin deposition occurs. In areas in which the skin has been greatly irradiated, ulcers appear. The ulcer caused by roentgen rays is characteristically punched out in appearance with a sharp edge and with a necrotic base. It is indolent, painful and intractable.

SYMPTOMS

All of our eighty patients with radiation dermatitis had such symptoms from the dermatitis as pruritis, burning and/or ulceration. Some thought they had cancer to a degree that they sought surgical consultation.

The effects of radiant energy on the skin are similar, regardless of the source of radiation, but vary quantitatively. The alpha ray produces the greatest histologic change and the effect of this is similar no matter what the source is. The more deeply penetrating gamma ray produces the least degree of cutaneous effect and the effect produced varies with the amount of radiation delivered, the amount of radiation absorbed, the time of exposure and the size of the field. The beta particle is intermediate in action.

TABLE 1
REASONS FOR IRRADIATION

Reasons	No. of Patients
Dermatitis, acne, psoriasis, trichiasis, etc....	41
Infection	8
Professional accidents	14
Hemangiomata	7
Miscellaneous: thyroid, keloid, nevus, etc...	10
Total	80

Various tissues respond in different degrees to an equal amount of radiation. According to DeCoursey [4], the skin is less sensitive than hemopoietic tissue, intestinal glands and gonadal epithelium; it is about as sensitive as the crystalline lens and cornea and more sensitive than fibrous tissue, cartilage, bone, muscle and nerves. The stratum corneum is the portion of the skin most resistant to radiation. The stratum germinativum is relatively sensitive, the hair follicles are extremely sensitive. The dose of radiation in man to produce permanent epilation is 700 r or more [6].

ANALYSIS OF CASES

Why Irradiation Was Given. A majority of the eighty patients were given radiation treatment for lesions that were cosmetically unacceptable in an attempt to improve the appearance of the patient (the results in this series indicate it would have been better if the original lesions had been allowed to remain). The lesions for which the radiation was given are included in Table 1.

Location. Listed in Table 11 are the locations of the various lesions; most of these lesions were on the head and neck. Most of the patients in the category "professional accidents" were

TABLE II
LOCATION OF RADIATION DERMATITIS

Location	No. of Patients
Head and neck	40
Trunk	6
Upper extremities	28
Lower extremities	8
Total	82*

* Two patients with two sites each.

TABLE III
DEVELOPMENT OF MALIGNANCY

Type	No. of Patients
Basal cell carcinoma	23
Squamous cell carcinoma	19
Basal and squamous cell carcinoma	3
Basal, squamous and fibrosarcoma	1
Total	46

NOTE: The average time from exposure to malignancy was twenty-seven years. The range was eight to forty years, with a standard deviation of 8.6 years.

doctors or dentists who were exposed while performing multiple diagnostic procedures on patients. In this group, most had an injury on the hands; some had an injury on the face from peering into fluoroscopes. Only one of the patients in this category was a nonprofessional person and the damage was sustained during a prolonged fluoroscopic search for a foreign body in the knee.

Development of Cancer. In the forty-six patients (57 per cent) in whom malignancy developed, the incidence of squamous and basal cell carcinoma is almost equal. (Table III.) Since in the general population the ratio of these tumors is approximately 5:1 in favor of the basal cell carcinoma, it appears that the irradiated skin offers a particularly favorable environment for the development of squamous cell carcinoma.

In this group of patients, the average and median period of time between the time of exposure and the diagnosis of malignancy was twenty-seven years. However, the range was from nine to forty years and the standard deviation was 8.9 years. In the group of thirty-four patients in this series who had not developed malignancy when first seen, the average and median period of time between exposure and the pathologic diagnosis of radiation dermatitis was twenty years, a range of three to forty years; the standard deviation was ten years.

Because of the large standard deviation, an accurate estimate of the time necessary for the development of malignancy cannot be made from these statistics, but the figures are generally in agreement with the results of Cannon [1]. It appears from this series that the danger of the development of malignancy is slight within the first ten years the radiodermatitis is present. However, in this series one of the worst cases encountered was the following. (Fig. 1.) Three malignant lesions developed in this patient (E. C.) in the area of radiation dermatitis; fibrosarcoma, squamous cell carcinoma and basal cell carcinoma developed within nine years of x-ray treatment. This patient died as a result of these diseases. Clinically, in most instances the patients with radiodermatitis who later developed cancer had a history of recurrent ulceration. Generally, they had more symptoms from the area of damaged skin than those patients in whom no cancer was found.

In the instances of patients with malignancy, there seemed to be no correlation between the development of malignancy and the pre-existing skin lesions. We could not have attempted a correlation between the amount and type of radiation administered inasmuch as the meager information available permitted no analysis. There was no correlation between the development of malignancy and the length of the period of x-ray treatment except the patients in this series generally received multiple exposures. There was no correlation apparent in regard to the appearance, extent of damaged skin and the development of the malignancy, or between the location of the radiodermatitis and the development of the malignancy.

TREATMENT

Treatment is surgical, dermatologic and psychiatric. In our eighty patients, the surgical treatment was usually excision of the affected area followed by grafting of the skin although occasionally simple excision and closure were

FIG. 3. Basal cell carcinoma of the face. Pre- (A) and postoperative (B) views.

possible. Amputation and/or coverage of the pedicle flap were required in many cases.

Probably, since the deeper tissues were often severely damaged too, there was a high incidence of failure of the initial graft. There was much oozing from fine teleangiectatic vessels when excision was performed, and hematomas occurred frequently and contributed to the incidence of failure of grafts.

Excision and skin grafting were used in the following instance. A physician, who had a fungus infection in his feet, was irradiated on two occasions three years apart. Fifteen years later, he was first admitted to the hospital with a two year old ulcer of his heel. A biopsy revealed a squamous cell carcinoma; a wide excision and a split skin graft were performed. (Fig. 2.) The primary healing was retarded; however, the patient has been well and free of disease for twelve years.

FIG. 2. Squamous cell carcinoma of the foot.

A more difficult therapeutic problem which involved grafting of skin was the case of a nurse who had had x-ray therapy for acne thirty years. She had multiple basal cell carcinoma of the face when first seen and it was necessary to excise most of the facial skin which was replaced by split skin grafts as shown. (Fig. 3A and B.) She has remained free from major disease for more than five years; with proper make-up her appearance is acceptable. The patient, whose hands are shown in Figure 4, was a dentist who used his fingers to hold x-ray film in patients' mouths for a number of years. He is still able to practice dentistry but is severely handicapped.

More involved surgical procedures were necessary for patients T. Q. (Fig. 5) and M. D. (Fig. 6). These patients were among the most severely diseased of the entire series.

T. Q. had acne and received x-ray treatment of his face twenty-eight years prior to admission. Treatment was given at weekly intervals for a year. He had a squamous cell carcinoma of the upper lip when first seen in this hospital ten years ago. Since then he has had twelve operations and/or hospital admissions and his appearance at the present time is

FIG. 4. Multiple squamous cell carcinoma of the fingers.

shown in Figure 5. Multiple basal cell carcinomas and additional squamous cell tumors of the mouth and palate have developed.

This patient has amazing fortitude and has maintained a stable attitude despite this severe disease. He has a moulage that was made by the Prosthetic Department of the University of Pennsylvania Dental School which has helped his appearance a great deal. Nevertheless he lost his job because of his appearance and has suffered severe economic losses. At present, all tumors appear to be controlled, but if there is extension into the sphenoid sinus and adjacent areas, further surgical procedure will be futile.

Patient M. D. had had x-ray treatment for facial hirsutism. An immediate severe reaction to radiation developed; thirty-five years later this progressed to a spontaneous laryngeal fistula and the development of squamous cell carcinoma involving the mandible. Despite radical surgery she died from the squamous cell carcinoma.

W. C. a 60 year old man, received radiation therapy of both hands for chronic dermatitis

FIG. 5. Squamous cell carcinoma of the face of patient T. Q.

FIG. 6. Squamous cell carcinoma of the face of patient M. D.

FIG. 7. Squamous cell carcinoma of the hand of patient W. C. Pre- (A) and postoperative (B) views.

thirteen years prior to admission. He had a squamous cell carcinoma, and by excising the forefinger and using the palmar surface as the pedicle flap a good functional and cosmetic result was obtained. (Fig. 7A and B.) He still has residual disease that requires occasional therapy but he has had no evidence of metastatic disease in over five years.

RESULTS

There have been five deaths in this group of patients. Three have died from metastatic radiation-induced tumor: E. C., M. D. and a radiologist who died from leukemia. One patient committed suicide when faced with the necessity of continued operations. One patient died from cardiovascular disease which was unrelated to the radiation dermatitis.

Of the living patients, one has inoperable spread from a squamous cell carcinoma, one has chronic myelogenous leukemia and one is in a nursing home with massive destruction of the face and nasal bones from an inoperable basal cell carcinoma.

Analysis of the seventy-two remaining patients revealed that only fourteen can be classed as being unaffected by the disease, either physically or socioeconomically. Three patients with major disability have been completely rehabilitated. Twenty-seven have some physical disability as a result of amputations, loss of tissue or functional impairment. Twenty-

eight patients must be classed as being disfigured cosmetically. Many of these patients have found it difficult to find and keep a job because of their appearance.

Fortunately, in the patients for whom it has been feasible to excise all of the damaged skin, malignancy has not occurred in the area of grafted skin and/or coverage of the pedicle flap. In the patients with residual damage of the skin, all suspicious lesions have been excised and a number of extremely small cancers have been controlled.

SUMMARY AND CONCLUSIONS

Eighty patients with radiation dermatitis following radiation for benign disease have been treated surgically. The surgical therapy of this disease has been difficult. Of this group, only seventeen patients may be classed as having had a satisfactory recovery from the disease. It is our plea that in the future, radiation will only be administered by a qualified radiotherapist and almost never for benign disease.

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Incompatible Blood Transfusion and Lower Nephron Nephrosis

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IT is well known that incompatible blood transfusions may result in renal damage in man [1]. Tubular nephrosis, however, has been much more difficult to produce in experimental animals by transfusion of incompatible blood. The purpose of this investigation was to learn whether the infusion of varying amounts of human blood directly into the renal arteries would influence the survival rate and resultant renal pathology, and whether similar injections in animals with hemorrhagic hypovolemia and dehydration would result in more uniform renal damage.

MATERIALS AND METHODS

Mongrel dogs of both sexes varying in weight between 8 and 14 kg. were used. They were anesthetized with 5 per cent sodium pentothal administered intravenously. Tracheal intubation was carried out, and rhythmic insufflation of the lungs with oxygen was maintained throughout the surgical procedure with a mechanical respirator. A left subcostal skin incision was made just distal to the twelfth rib, the muscles were split and the aorta exposed extraperitoneally at the level of origin of both renal arteries. The abdominal aorta proximal and distal to the renal branches was occluded by means of noncrushing vascular clamps until the intra-aortic infusion was completed. Human whole blood preserved in standard acid-citrate-dextrose solution was obtained from the blood bank and administered in measured amounts. Blood types A, B and O were used. Blood was obtained from different donors, but not mixed prior to administration. The blood was injected rapidly and directly into the renal segment of the aorta. Thus all the infused blood passed through the two renal arteries except the small amount which escaped through the lumbar arteries located between the clamps.

One group of five dogs were injected with 50 cc. of saline solution in the same manner and served as controls. Nine other groups of from five to ten dogs received, respectively, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 9, 12.8 and 18.1 cc./kg. of human blood. Following the injection, the cephalad clamp was released first and then the distal one. Pulsation of the renal arteries was confirmed by palpation after the clamps were removed. The incision was closed and 300,000 units of procaine penicillin was administered intramuscularly.

Three additional groups were studied by similar administration of 6.4 cc./kg. of human blood or saline solution immediately after the rapid removal through a femoral catheter of 20 cc./kg. of blood. In one group, saline solution was administered and in the other two, blood. Dogs in one of the latter two groups were dehydrated, in addition, by withholding all food and water for twenty hours prior to and twenty-four hours after transfusion.

All the dogs were observed carefully afterwards. Those which survived were kept for two weeks and sacrificed by intravenous injection of excessive amounts of sodium pentothal. The kidneys from all but four dogs were examined grossly and microscopically.

RESULTS

A few minutes after the infusion was started, the pulse rate of most animals increased. A

TABLE I
RESULTS FOLLOWING TRANSFUSION OF INCOMPATIBLE BLOOD INTO RENAL ARTERIES

Amount of Incompatible Blood Injected (cc./kg.)	No. of Dogs Studied	No. of Dogs Which Died Within Eighteen Hr.	No. of Dog Which Survived for Fourteen Days
Control (50 cc. of saline)	5	0	5
0.2	5	0	5
0.4	5	0	5
0.8	5	0	5
1.6	5	0	5
3.2	5	0	5
6.4	5	0	5
9.0	7	2	5
12.8	9	4	5
18.1	10	5	5

hemorrhagic tendency generally appeared and bleeding occurred from the edges of the incision, especially in those which received more than 6.4 cc./kg. of blood. Following injection of the heterogenous blood, the majority of dogs awakened prior to the following day, recovered and were normally active.

The results following the transfusion of blood are presented in Table 1. None of the dogs in the control group and in those groups which received 6.4 cc./kg. of blood or less died following the procedure. However, two of the seven dogs receiving 9 cc./kg., four of those receiving 12.8 cc./kg. and five of those given 18.1 cc./kg. died within eighteen hours after surgery. Among them, one which was given 9 cc./kg. and three given 18.1 cc./kg. died on the operating table, cardiac arrest occurring five to twelve minutes after the injection was started. The remainder of the animals, five in each group, survived until they were sacrificed on the fourteenth postoperative day. Their activities appeared normal.

The results in the dogs bled immediately prior to transfusion and in those dehydrated and bled are presented in Table II. There was one death in the control group within twenty-four hours of the experimental procedure. Two dogs which were bled but not dehydrated died, one on the fourteenth and one on the fifth day following the transfusion. One dog which was bled and dehydrated died three days after transfusion. The remainder were sacrificed on the fourteenth day.

TABLE II
RESULTS FOLLOWING TRANSFUSION OF INCOMPATIBLE BLOOD INTO THE RENAL ARTERIES OF DOGS SUBJECTED TO BLOOD REMOVAL AND DEHYDRATION

Test Procedure	No. of Animals Studied	No. of Deaths	No. Sacrificed
Removal of blood Infusion of normal saline solution (6.4 cc./kg.)	9	1	8
Removal of blood Transfusion of blood (6.4 cc./kg.)	9	2	7
Removal of blood, dehydration. Transfusion of blood (6.4 cc./kg.)	10	1	9

PATHOLOGIC FINDINGS

The kidneys from the animals sacrificed and those which died were fixed in neutral 10 per cent formalin solution. One block including both cortex and medulla was taken from each kidney. They were embedded in paraffin in the usual manner, sectioned at 6 μ. on a rotary microtome and stained with hematoxylin and eosin.

In only two dogs, both from the group bled immediately before transfusion, were the histologic findings typical of lower nephron nephrosis. They consisted of hemoglobin casts in the tubules in the region of the corticomedullary junction, with degenerative changes in the adjacent renal tubular epithelium. (Fig. 1.) Polymorphonuclear leukocytic and lymphocytic infiltrates surrounded these tubules. In addition, extrusion of some of the material of the casts into the surrounding interstitial tissue was observed. (Fig. 2.) These changes resemble the lesions of lower nephron nephrosis as described by Lucke [2].

In addition, in thirty-one of the remaining ninety animals studied, varying degrees of interstitial fibrosis with mononuclear infiltration were noted. (Fig. 3.) These areas of fibrosis frequently contained dilated tubules lined by flattened epithelial cells. Some of the dilated tubules contained proteinaceous and orange casts apparently containing hemoglobin. Such orange casts were seen only in those animals which had been injected with blood. No inter-

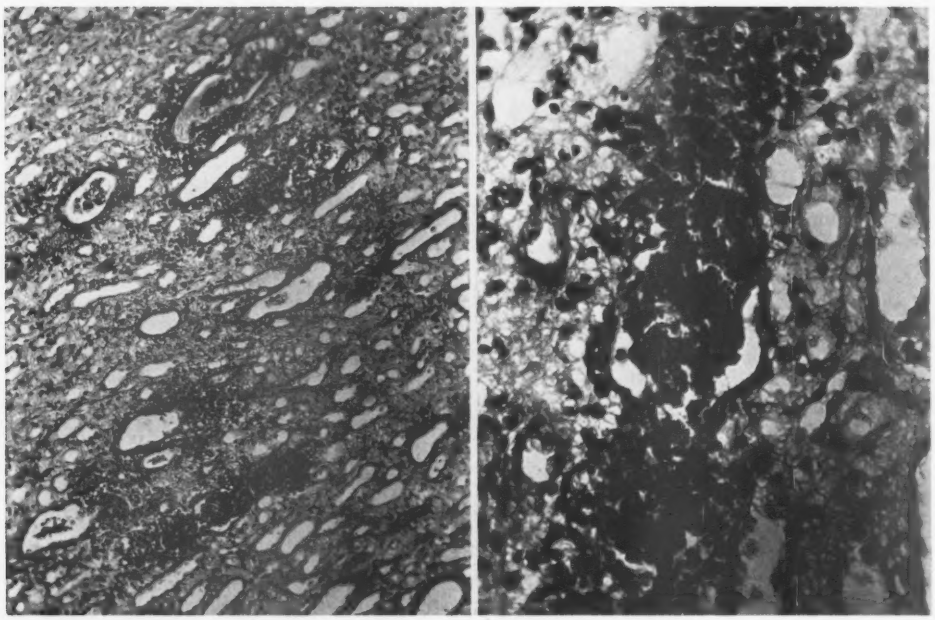

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FIG. 1. Low power view of the corticomedullary junction showing granular hemoglobin casts in renal tubules, flattened tubular epithelium and polymorphonuclear and mononuclear infiltrates surrounding the tubules.

FIG. 2. High power view of one of the tubules seen in Figure 1 showing extrusion of some of the material of the cast into the surrounding tissue.

stitial reaction to the orange material in the tubules was detected. The fibrosis and cellular infiltration were more prominent in the cortices than in the medullary areas, and in a few instances were associated with foci of interstitial calcification. These lesions are thought to represent the effects of interstitial nephritis which occurs in most dogs over eight years of age [3]. Both animals with changes of lower nephron nephrosis also exhibited moderate degrees of interstitial nephritis.

The changes of interstitial nephritis were most frequent and most pronounced in the animals receiving the largest amounts of blood. Furthermore, in the kidneys removed from twenty-one animals sacrificed in the course of experiments not involving the kidneys, only slight or moderate interstitial nephritis was found in only three animals. On the other hand, the mature appearance of the fibrous tissue and the presence of calcification in a few instances suggest that at least some of the lesions in the experimental group antedated the injection of blood and were probably not related to it.

COMMENTS

The injection of heterologous blood into the renal arteries of dogs failed in our experience to produce lower nephron nephrosis. When this was preformed in dogs in which moderate hemorrhagic hypovolemia was present, this pathologic change developed in a very small percentage. Dehydration in addition to hypovolemia was not followed by nephrosis. Interstitial nephritis was observed far more commonly in dogs receiving heterologous blood than in those sacrificed after unrelated experiments. Furthermore, such changes occurred more frequently in those which were given large renal artery transfusions. On the other hand, some of the pathologic alterations seen as a part of this picture suggested that they antedated the experiment. Few of our animals died as the result of transfusion with incompatible blood and these deaths occurred following fairly large transfusions.

Generally others have also failed to produce renal tubular damage with any regularity. Conn and his associates [4] reported that a single

intravenous transfusion of 7.5 cc./kg. of whole human blood in dogs was not followed by death and produced no marked renal lesions. Mueller and Mason [5] administered 100 to 200 cc. of human blood to dogs intravenously without anesthesia. The dogs survived and biopsies of the kidneys revealed no evidence of pathologic changes in the renal tubules. Hardaway and his colleagues [6] gave dogs an intravenous transfusion of human whole blood. In two instances in which 100 and 114 cc., respectively, were injected rapidly, death occurred within twelve minutes. After the slow injection of from 191 to 367 cc., four dogs died or were sacrificed in eighteen hours, twenty-six hours, three days and eight days. Thrombi were seen in the renal vessels of those dogs to which the blood was given rapidly. In the cases in which the injection time was prolonged, hemoglobin and red blood cell casts were found in the tubules of most of the animals, no thrombi were found and tubular necrosis was observed in only one instance. There was no clearcut evidence that the deaths were due to renal failure, and it was suggested that the sudden deaths may have been due to cessation of pulmonary blood flow with the sudden development of acute cor pulmonale. McKay and his group [7] injected stored human blood into the aorta of ten dogs through a catheter inserted through a femoral artery with its tip located at a point approximately 2 cm. above the renal arteries. Between 50 and 300 cc. of heterogenous blood were injected quickly. Successive biopsies of the kidneys were performed in seven of ten animals. None of the dogs survived the transfusion more than five days, and the seven in which successive biopsies were performed all died within ten and a half hours. At autopsy the surface of the kidneys revealed numerous dark flecks resembling petechiae and tubular necrosis in the subcapsular cortex with hemoglobin casts in a few surrounding tubules. In addition, one kidney revealed focal necrosis in a few scattered tubules in the juxtamedullary cortex. Capillary thrombi were seen in most of the kidneys. Hemoglobin casts were found in variable numbers in most of them and focal tubular necrosis occurred in two. Death of the animals was thought primarily due to thromboses in the pulmonary vascular bed. In unpublished work Rhamy and his associates [8], however, were more successful in producing nephrosis. They, too, studied the effects of intra-aortic infusion of stored human whole blood in dogs. From 5 to 10 cc./kg. of body weight were injected rapidly through a catheter inserted through a femoral artery, the tip of which was placed at the level of the renal arteries and its proper location confirmed by laparotomy. One kidney was subjected to repeated biopsies. Sudden hypotension developed in some of the dogs and they died on the operating table. The remaining animals died within a week, and at postmortem examination the changes of lower nephron nephrosis were observed.

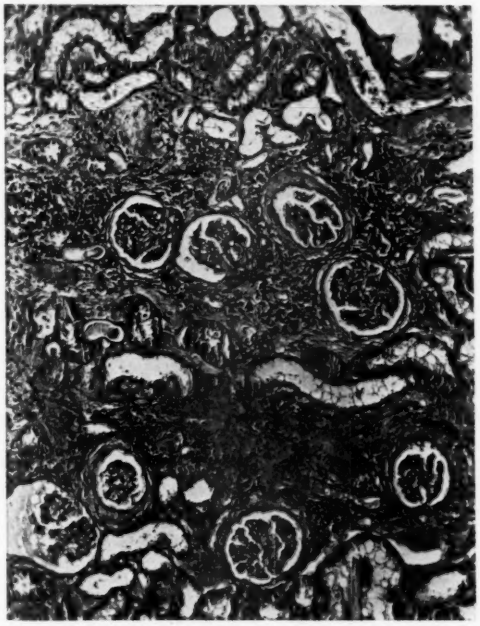

FIG. 3. Section of kidney illustrating chronic interstitial nephritis. Note the fibrosis with mononuclear infiltration and the tubules with flattened epithelium and proteinaceous casts in the lumens.

Since we were unable to produce lower nephron nephrosis in dogs receiving large amounts of whole human blood directly into the renal arteries, we investigated this procedure with acutely induced moderate hemorrhagic hypovolemia. This was done because of the known reduction in renal blood flow which follows acute hemorrhage, the alteration of renal function, and, in humans, the development of lower nephron nephrosis. We did not succeed in producing lower nephron nephrosis regularly in these animals, but it is of interest

that the only two dogs with typical findings of lower nephron nephrosis were in this group.

We also thought it important to study the effects of incompatible blood transfusion into the renal arteries in other dogs rendered hypovolemic and dehydrated. Lalich [9] had produced lower nephron nephrosis in rabbits by depriving them of food and water for three days and giving them, during the next three days, seven to ten intravenous injections of hemologous hemoglobin equal to 1.8 cc./kg. of weight. During this period the animals were without food and the only water they received was administered intravenously (22 to 38 cc. daily). Approximately one third of the rabbits died of hemoglobinuric nephrosis while the two thirds which survived had elevated nonprotein nitrogen. Left nephrectomy was performed from thirteen to seventeen days after the initial injection of hemoglobin in the surviving animals. When they were sacrificed from thirty-four to 116 days later, gross and microscopic study revealed hemoglobinuric nephrosis in each instance. Baker and Dodds [10] succeeded in producing lower nephrosis only in rabbits with urinary acidity following the intravenous injection of hemoglobin. They believed that two factors, increase in acidity and in salt concentration, together caused precipitation of the hemoglobin which, in turn, mechanically plugged the tubules. DeGowin and his coworkers [11] who gave repeated injections of large amounts of laked red blood cells to dogs made observations which appeared to confirm the findings of Baker and Dodds. Their study led them to believe, however, that in addition to plugging the renal tubules by hemoglobin pigment, there was also an unexplainable nephrotoxic process which could cause renal insufficiency independent of and in the absence of mechanical obstruction of the tubules by precipitated hemoglobin. On the other hand, some observers, for example de Navasquez [12], have failed to reproduce the results obtained by Baker and Dodds. In our own experiments we found no tubular nephrosis following the intrarenal arterial transfusion of human blood into hypovolemic and dehydrated dogs. Although some of the discrepancies can possibly be explained on the basis of differences in technic and animal species, it seems safe to conclude that hemoglobin is precipitated with great difficulty in the normal kidney of experimental animals and especially in those of dogs.

Our own experiments suggest that large incompatible blood transfusions, even when administered directly into the renal arteries of normal dogs and in dogs with moderate hypovolemia and moderate dehydration, will not result regularly in renal nephrosis. Indeed, in only two of our animals, both given large amounts of blood immediately following hemorrhage, did these changes develop.

SUMMARY AND CONCLUSION

Varying amounts of human blood were infused rapidly into the renal arteries of sixty-one dogs. No animal receiving 6.4 cc./kg. or less died. Several receiving larger amounts of blood died during the first eighteen hours. Typical findings of lower nephron nephrosis were not observed when the animals were sacrificed two weeks after the transfusion.

Nine animals were given 6.4 cc./kg. of human blood into the renal arteries following removal of 20 cc./kg. of blood. In another group of ten animals the same amount of blood was administered in the same fashion to dehydrated animals bled 20 cc./kg. Only two animals died and the remainder recovered uneventfully. Lower nephron nephrosis was observed only in two of the first group.

Lesions compatible with interstitial nephritis were noted in thirty-one dogs. The severity of this lesion and its incidence tended to be greater in those animals which had been given the larger amounts of blood. Similar lesions were observed, although much less frequently, in animals sacrificed following unrelated experiments. Some of the pathologic findings associated with interstitial nephritis, however, suggested that they may have antedated the blood transfusion.

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Experiences with Large Infusions of Gamma Globulin

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Interest in the intravenous administration of large amounts of gamma globulin has developed for several reasons. Moore and Amos [9] have reported on their experiences with large doses of gamma globulin as a potential source of a humoral factor which might inhibit the growth of malignant neoplasms. Several investigators have reported that, alone or in combination with certain antibiotics, gamma globulin may have a favorable effect in the treatment of refractory infections, particularly those in which pseudomonal or staphylococcal organisms are involved [1–3,8,12]. Thirdly, the possibility of adding gamma globulin to blood transfusions as a potential prophylactic agent against the virus of homologous serum jaundice has been considered. Finally, the effect of large amounts of circulating gamma globulin on the intravascular distribution of other plasma proteins has not been well defined.

The chief limitation in the clinical use of intravenous gamma globulin has been a significant incidence of "colloidal" reactions. In addition, since the cost of preparation of this agent is appreciable, a clearly defined clinical benefit must be demonstrated before one would be justified in recommending the use of such large volumes of material.

This is a report of our experience with the administration of gamma globulin, in amounts totaling 100 to 450 gm., to five selected patients with far advanced malignant neoplasms. Also reported are our observations concerning changes in the neoplasm, associated infection and serum protein levels and the results of our efforts to modify colloidal reactions. Several more recent attempts to modify reactions with albumin are also reported.

METHODS

Since the reactions to infusions of gamma globulin may be quite unpleasant, only patients with far advanced malignant neoplasms who could conceivably benefit from such therapy were selected. All patients had received other forms of palliative therapy for advanced cancer and had been rejected for further treatment. Treatment with gamma globulin was instituted in one patient with acute leukemia primarily to observe its effects in the treatment of a refractory staphylococcal infection rather than for its possible effect on the neoplasm.

Serial infusions, usually daily, of gamma globulin were given in doses of 4.9 to 75 gm. per infusion. The gamma globulin was diluted in varying amounts of 5 per cent dextrose in water or 5 per cent dextrose in saline and infused at rates of .05 to 3.3 gm. per minute.

Blood specimens were obtained prior to a course of therapy and prior to each infusion for serum protein fractionation. On a number of occasions, specimens were obtained immediately after infusion. Serum proteins were fractionated by the method of Wolfson et al. [14].

Attempts were made to modify reactions with various sedatives, with antihistamines and with a mixture of an emulsifying agent, alcohol and glycerol (Pluronic® F68, 2.5 per cent*; ethanol, 6.4 per cent; and glycerol, 5 per cent) as recommended by Waddell et al. [13]. More recently albumin has been evaluated as a stabilizing agent.

Histologic examination of neoplastic cells

* Pluronic F68 was kindly supplied by the Wyandotte Chemical Company, Wyandotte, Michigan.

TABLE 1

SUMMARY OF DATA OBTAINED DURING EXPERIENCES WITH LARGE INFUSIONS OF GAMMA GLOBULIN

Patient	Diagnosis	Gamma-2 Globulin Levels (gm. %)			No. of Reactions/ No. of Infusions	Total Dose of Gamma Globulin (gm.)
		Preinfusion	Maximum	Postinfusion		
E. B.	Hodgkin's disease (sarcoma type	0.37	3.68	0.41 (5 weeks)	6/15	380
O. W.	Hodgkin's disease (sarcoma type)	0.10	0.93	Died	2/7	188
M. W.	Metastatic melanoma	0.31	1.50	0.29 (3 weeks)	6/15	400
J. M.	Acute leukemia, pyoderma gangrenosum	1.36	2.17	1.08 (2 weeks)	4/25	450
H. S.	Multiple myeloma	...	...	Died	0/4	100

was carried out immediately preceding and following therapy in all cases. Death occurred in all patients within several months of the termination of therapy, and the results of postmortem examination were obtained in each instance.

RESULTS

Knowledge of the reactions to be expected prompted us to begin our infusions in the first patient with relatively small doses of gamma globulin in large volumes of 5 per cent dextrose in water. Daily doses were progressively increased from 5 to 75 gm. and the total volume of infusion was decreased since the degree of dilution of this agent did not seem to be a critical factor influencing reaction rate. Reactions consisted of one or more of the following symptoms: apprehension, headache, transitory visual difficulty, constricting pain in the anterior portion of the chest, shortness of breath, nausea, vomiting, fever, shaking chills and pain in the abdomen, back and thighs. Eight of the total of eighteen reactions during sixty-six infusions included a majority of the aforementioned symptoms and were considered to be "major" as far as discomfort of the patient was concerned. The others were "mild," usually characterized by slight pain in the chest or back or fever. In no patient did any significant change in blood pressure take place other than an occasional slight rise. Several reactions occurred after less than 2 gm. gamma globulin had been infused.

After cessation of the infusion following the onset of the first two reactions, it was discovered that the infusion could be slowed, the reaction allowed to subside and the infusion then could be resumed without further reaction or with recurrence of only minimal symptoms. Subsequently, administration of the predetermined dose was always possible after the infusion had been slowed to allow the reaction to subside. Several different lots of gamma globulin were used with no demonstrable difference in the reaction rate. Provided in Table 1 is a brief summary of data with respect to diagnosis, changes in gamma-2 globulin, total dosage and reaction rate. Gamma-2 globulin corresponds to classic gamma globulin as detected by moving boundary electrophoresis.

Ten of the eighteen reactions occurred with the first several infusions given in the course of treatment of four of the five patients receiving this agent (patient H. S. was semicomatose at the time the course of therapy was instituted and had no visible reaction during the four infusions he received prior to his death). Although a slower rate of infusion did not seem to have any influence on the prevention of reactions, it did appear to influence the frequency of recurrence of symptoms once a reaction had occurred and the infusion was resumed.

None of the medications initially used in an attempt to limit reactions appeared to have any effect other than some suppression of the severity of the reactions by sedation. No apparent difference in reaction rate was observed when pretreatment with the Pluronic F68 mixture was attempted.

More recently we have been interested in the

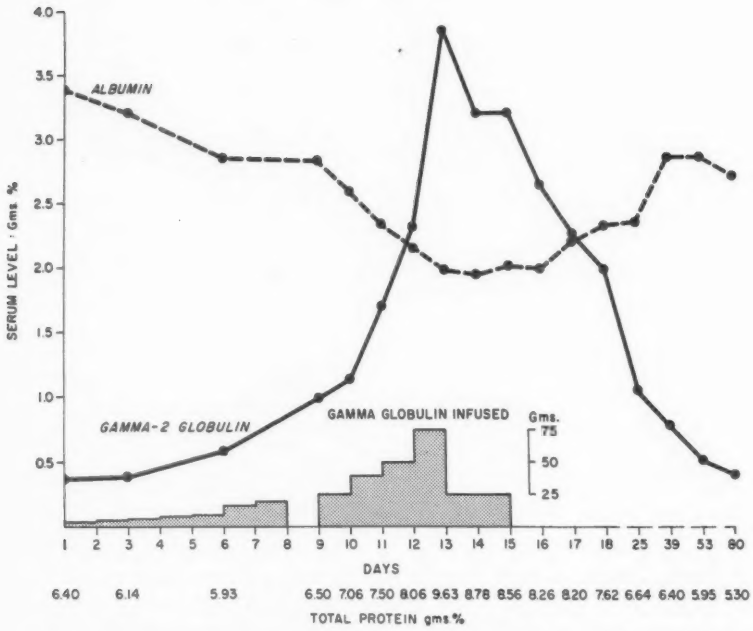

FIG. 1. Depicted above are changes in the levels of serum gamma-2 globulin and albumin in patient E. B. during and following serial infusions of gamma globulin.

possible use of albumin as a stabilizing agent. Mixtures of albumin and gamma globulin have been given to three patients (two with advanced metastatic adenocarcinoma and one with fulminating gram-negative septicemia). All patients were conscious and well oriented. Two patients received two infusions, each of 25 gm. of gamma globulin, and the third received one infusion of the same amount. Only several infusions were given to these patients since the majority of reactions occurred during the administration thereof. Albumin was added to each infusion in amounts of 6.4 to 25 gm. In three of the five infusions, no reaction of any kind was observed. After one infusion no colloidal reaction occurred but a delayed pyrogenic reaction (temperature of 102°F.) took place one hour after infusion was completed. The third patient, receiving an infusion of 25 gm. gamma globulin and 12.5 gm. albumin, had malaise and a headache after approximately 6 gm. gamma globulin had been administered. This apparent reaction might have been prevented if a higher concentration of albumin had been used. Although the use of albumin as a "stabilizing agent" does not appear to be uniformly successful in suppressing colloidal reactions in the concentrations used, these experiences are somewhat encouraging since reactions were observed during each of the first two infusions to the four conscious patients who had received this agent previously.

No alteration in the course of the neoplastic disease was noted in any of the patients. The patients E. B. and M. W. had visible ulcerative neoplasms; slight progression in the size of the neoplasms was observed during the course of therapy. Biopsies or cytologic examinations were performed immediately preceding and following treatment in each patient; no change in character of the neoplastic cells was noted. All patients died one day to three months after the course of therapy was completed; no pertinent alterations in the growth or character of the neoplasms were found during autopsy.

Although J. M. had acute myelocytic leukemia, therapy with gamma globulin was instituted to study its possible synergism with chloramphenicol in the treatment of a refractory staphylococcal infection (coagulase-positive hemolytic Staphylococcus aureus, no phage type was determinable) [3]. Five months

previously, the first diagnosis of acute leukemia was made for J. M. Treatment with 6-mercaptopurine resulted in an excellent hematologic response. Three months previously, a progressing pyoderma gangrenosum, involving the buttocks, back, thighs and abdomen, had developed. Treatment with Furaltadone® (nine weeks), penicillin, ristocetin and chloramphenicol had had no effect on the gradual progression of the lesions. At the time of gamma globulin therapy, chloramphenicol was again administered in a dosage of 2 gm. daily. After several days of therapy, regression in the size of the skin lesions was noted; only one new lesion developed during the subsequent course of twenty-five infusions, and the lesions remained stationary for the remaining one month of the patient's life.

An interesting reciprocal relationship between serum levels of albumin and gamma-2 globulin during the period of serial infusions was noted in all patients. It was the most striking in E. B., who had the greatest elevation in serum gamma-2 globulin during therapy. (Fig. 1.) Changes in the other protein fractions were insignificant or minor in comparison to changes in the albumin and gamma-2 fractions.

Plasma volume was determined and protein fractionation of serum was carried out immediately before and after an infusion to one patient. By this technic, an estimate of the infused gamma globulin retained in the intravascular space at termination of the infusion could be obtained. Thus, 17.4 gm. of a 25 gm. dose of gamma globulin was estimated to be intravascular by this method; the simultaneous decrease in the level of albumin indicated an apparent loss of approximately 6.8 gm. albumin from the vascular space.

The higher the elevation of gamma-2 globulin levels over pretreatment values, the longer the time required for return of elevated gamma-2 globulin levels to within normal limits. Of the three patients from whom serial determinations of serum proteins could be obtained after cessation of therapy, the serum gamma-2 globulin levels decreased about 50 per cent in one week and returned to pretreatment levels or below in two to five weeks.

COMMENTS

If the problem of reactions to infusions of gamma globulin could be solved, the potential usefulness of this protein might be enhanced. An investigation into the efficacy of pooled gamma globulin added to blood prepared for transfusion as a possible prophylactic agent against homologous serum jaundice would be indicated only if one could be assured that no appreciable incidence of reactions were associated with such a regimen.

Similarly, considerable data have been presented to support the concept that administration of gamma globulin alone or in combination with chloramphenicol may have real benefit in the treatment of infections indigenous to the population from which the pool of gamma globulin is obtained [*1–3,8,11,12*]. Although gamma globulin may be given by multiple intramuscular injections, the amount which can be given by this route is limited to 5 ml. (0.82 gm.) per injection. Since the amount of specific antibody supplied is related to the total dose, much larger doses might have considerably greater efficacy particularly in supplying antibodies to infectious organisms relatively uncommon in a population. This reasoning is of practical importance in the treatment of Pseudomonas septicemia, a common cause of death in patients with severe burns [*7*]. Although the "frightening" reactions to intravenous administration of gamma globulin should not restrict the use thereof in a patient with a potentially fatal infection, these reactions are responsible for added morbidity. The favorable response of our leukemic patient with pyoderma gangrenosum, who was totally unresponsive to prolonged therapy with multiple antibiotics, has encouraged us to consider the future use of gamma globulin in patients with Ps. septicemia and refractory staphylococcal infections.

Although our primary interest in this study was the investigation of colloidal reactions and protein distribution after large infusions of gamma globulin, selection of patients with certain far advanced neoplasms permitted us to expand somewhat on the series reported by Moore and Amos [*9*]. These authors and Hauschka [*5*] have discussed in considerable detail the possible immunologic aspects of cancer. Like Moore and Amos, we found no detectable alteration in the neoplastic lesions of any of our patients following the infusion of pooled gamma globulin. This does not exclude a possible beneficial effect from more specific antiserums.

The fundamental nature of the reactions to

intravenous gamma globulin has not yet been clarified. These reactions bear a striking resemblance to those observed after intravenous administration of colloidal iron [*10*], fat emulsions [*13*] and occasionally plasma. The uniform characteristic of this type of colloidal reaction is that slowing of the infusion will result in gradual subsidence of the reaction following which the infusion may be completed, usually with few or no further symptoms.

Waddell et al. [*13*] have discussed in some detail the possible etiology of colloidal reactions to intravenous administration of fat emulsions. The most logical explanation, which has not been substantiated *in vivo*, is that on introduction of colloidal material into the blood stream there is an interfacial reaction leading to aggregation of colloidal particles; these flocculated particles produce transient ischemia which is relieved as the aggregates disperse. Most of the symptoms of colloidal reactions could be explained on the basis of transitory occlusion of small vessels by colloidal aggregates (anginoid type of pain in the chest, pain in the bones of the vertebral column, pain in the abdomen, dyspnea, and transitory visual difficulty among others). Leveen et al. [*5*] have shown *in vitro*, that globulins "break" purified fat emulsions, causing coalescence of fat droplets; since the 16 per cent solution of gamma globulin used in these studies is concentrated approximately twenty-five times more than in plasma, this colloid could produce a coalescence of circulating chylomicrons. Since albumin produces the opposite effect of stabilizing fat emulsions, this might provide an explanation why colloidal reactions to infusions of plasma occur much less frequently.

Our attempts at preventing or suppressing colloid reactions were largely unsuccessful. Antihistamines administered before or with the infusion had no effect. Heavy sedation suppressed the severity of the symptomatic response but appeared to have no effect on alteration of the incidence of reactions. Waddell et al. [*13*] have reported considerable success in eliminating colloidal reactions by infusing a mixture of Pluronic F68, alcohol and glycerol prior to the first infusion of fat emulsion. At least in this small group of patients, prior infusion of 100 ml. of this mixture had no apparent affect on reduction of the incidence of these reactions to intravenous administration of gamma globulin. Our experiences with addition of albumin are somewhat more encouraging, but additional data with respect to optimal concentrations would be useful.

As might be expected, the rate and degree of rise in serum gamma globulin could not be directly related to the dose administered. Of the many variables which might influence this process, probably the most important was the poor nutritional status and inadequate food intake of the majority of these patients. Patient E. B. had the most satisfactory dietary intake and also the greatest rise in serum gamma globulin.

Of interest is the apparent effect on serum albumin of large amounts of gamma globulin. The reciprocal decrease in albumin concentration occurring coincidently with the rise in gamma-2 globulin levels could not have been solely on oncotic response to expansion of plasma volume since alpha and beta globulin levels did not decrease in proportion to the decrease in the levels of albumin; alpha and beta globulin levels remained unchanged or, on several occasions, actually rose slightly. Some physiologic mechanism may control maximal serum protein concentration. Gray and Guzman Barron [*4*] postulated that the high levels of serum gamma globulin in patients with cirrhosis of the liver might arise secondarily as a compensatory mechanism to offset the decrease in plasma oncotic pressure associated with hypoalbuminemia. These data make the contrary hypothesis equally acceptable; increased production of gamma globulin with consequent elevated serum levels may result in a secondary fall in the levels of serum albumin.

SUMMARY

The possible clinical applications for large infusions of gamma globulin have been discussed. Our data confirms that of Moore and Amos with respect to the absence of chemotherapeutic value of pooled gamma globulin in patients with far advanced malignancy. Of greatest practical importance, at present, is the use of gamma globulin as a potential source of specific antibody against organisms producing infections refractory to therapy with antibiotics alone; an apparent therapeutic benefit in one such case is reported. The definitive cause and method for suppression of colloidal reactions to infusions of this agent have not yet been found. Since these reactions have not produced

any serious sequellae to date, we see no objection to the cautious intravenous infusion of gamma globulin in patients with refractory infections. The addition of albumin to the infusion may have a favorable effect on reduction of the incidence and severity of reactions.

The reciprocal fall in the level of albumin secondary to the elevation in the level of circulating gamma globulin presents an interesting theoretic implication with respect to factors controlling the level of circulating plasma proteins.

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Treatment of Chronic Nonspecific Ulcers of the Leg with Adenosine-5-Monophosphate

A CONTROLLED STUDY

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CHRONIC, nonspecific ulcers of the leg are difficult to treat in spite of modern therapeutic methods. Experience has demonstrated that best results are obtained by compression bandages, Unna boots and elevation of the extremity which increase the movement of lymph and venous blood away from the ulcer. To be effective, however, these measures require persistent application on the part of both patient and physician. For this reason there has been a continual search for some agent that, when ingested, injected into or rubbed on the ulcer, will bring about healing in a short time, thus obviating the necessity for bandages and boots.

In 1949, Rottino [6] described the use of adenosine-5-monophosphate (A5MP, muscle adenylic acid) in cases of pruritis. Later Rottino, Boller and Pratt [7] reported improvement in patients with phlebitis and ulcers in the leg treated with muscle adenylic acid. Subsequently, other reports [1–4] appeared attesting to the therapeutic value of this agent in a variety of vascular conditions. These clinical observations received support from the work of Reynolds and associates [5] who were concerned with the healing of wounds in the rat. In this study, A5MP was administered to groups of animals under metabolic and steroid stress as well as that caused by mechanical means. It was concluded that "A5MP may be effective in decreasing the lag interval of wound healing."

Adenosine-5-monophosphate is of fundamental importance in such biologic mechanisms as glycolysis, the Kreb's cycle and muscle activity. Adenosine-5-monophosphate possesses the high energy phosphate bonds necessary for restoration of energy which is constantly drained by the physiologic activity of functioning tissues. In addition to its role in carbohydrate metabolism and muscle activity, A5MP is intimately related to peptide and urea synthesis, fatty acid oxidation and nerve impulse transmission. It was these properties which led to the assumption that this agent may affect healing of chronic wounds.

In an effort to evaluate the effectiveness of adenosine-5-monophosphate in promoting healing of ulcers of the leg, a study was initiated in the Tulane Vascular Clinic, Charity Hospital of Louisiana at New Orleans. This report is concerned with the results of this study.

MATERIAL AND METHODS

A double blind study was set up in the following way. Four groups of ampules were supplied by the manufacturer,* two of which contained sustained action A5MP, 10 mg. per ml., and two contained only the vehicle, a gelatin-phenol solution which was identical in appearance and consistency with A5MP. Each of these four sets of ampules was labeled with a code symbol as follows: Ba, Po, Kn and Mr. Neither the physicians in charge of the study nor the nurses administering the medication knew the correct code designation.

All patients were treated on an out-clinic basis. The agent was administered intramuscularly in a dose of 1 ml. three times a week. When selected for the study, each patient was placed in a category denoted by code letters. For the

* Miles-Ames Laboratories.

next three months or until complete healing occurred, if this required less than three months, the same agent was administered. If healing had not taken place at the end of three months the patient was changed to another code category. By this method of assignment, patients were divided into four groups and at the end of a year those receiving therapy throughout the year had passed through each of the four therapeutic categories.

In addition to drug therapy, patients were carefully instructed in local care of ulcers of the leg. Care at home consisted of maintaining cleanliness of the leg and employing compression bandages. Patients were instructed to change the dressing over the ulcer every two or three days, depending on the amount of drainage, and to wash the ulcer area thoroughly with mild soap and water before applying a new dressing. The dressings consisted of white petrolatum applied directly to the ulcer and covered by a layer of gauze cut from a roller bandage, followed by a layer of cellulose cotton wrapped around the leg for absorption and padding. This, in turn, was covered with a rubber elastic bandage applied snugly around the leg at the level of involvement. Patients were examined in the clinic as often as three times a week, if necessary, to make certain that they understood the methods of and necessity for local care of the ulcer.

When an ulcer had healed, the elastic bandage and dressing were discontinued and replaced by a heavy weight elastic stocking. Careful attention was paid to proper fitting of the stocking, and the extent to which it prevented the formation of edema was taken as an indication of its adequacy.

As just indicated, each course of therapy lasted three months. At the start of treatment, the duration of the ulcer was recorded and the size and depth of the ulcer were estimated. Ulcers were classified as *small* (1 by 1 cm. or less), *medium* (1 by 1 cm. to 3 by 3 cm.), *large* (3 by 3 cm. to 5 by 5 cm.) and *extra-large* (5 by 5 cm. and over). The ulcer was considered to be superficial if islands of epithelium were present, or deep if the ulcer base consisted of granulation tissue alone. Colored photographs were taken of the ulcers at the beginning and at the end of each course of therapy. Progress during each course of therapy was determined by observations made at each visit to the Clinic and from the photographs. The following system was used in estimating the extent of healing during treatment.

TABLE 1
AGE DISTRIBUTION OF PATIENTS WITH ULCERS OF THE LEG

Age (yr.)	No. of Patients
20 through 29	2
30 through 39	9
40 through 49	17
50 through 59	15
60 through 69	28
70 through 79	8
80 through 89	1
Total	80

(++) The rate and extent of healing was greater than that which might be anticipated from the application of proper pressure dressings alone.

(+) The rate and extent of healing was no greater than that which might be anticipated from local care alone.

(o) No change in the appearance of the ulcer occurred.

(−) There was an actual increase in the size of the ulcerated area during treatment.

The results were assembled on the basis of the four code categories, the code was then broken and the actual results determined.

During the period from August 1957 through July 1959, 160 patients were admitted to the study group. In order to achieve some degree of uniformity, patients with an ulcer of the leg associated with peripheral arterial disease were excluded and only those with chronic ulcers following thrombophlebitis or trauma were considered. Furthermore, patients who failed to cooperate by following instructions for local care of an ulcer and those receiving less than one half of a course of therapy were dropped from the study. Consequently, among 160 patients, only eighty or 50 per cent fulfilled the criteria for inclusion in this series; they form the basis for this report.

RESULTS

The majority of patients were in the fourth, fifth and sixth decades of life, the range being from twenty to eighty-five years. (Table 1.) There were twenty-nine men and fifty-one

TABLE II
RESULTS OF THERAPY FOR ULCERS OF THE LEG

Degree of Healing*	No. of Courses Using A5MP†	No. of Courses Using Placebo†
++	28 (26.7)	26 (21.8)
+	40 (38.1)	45 (37.8)
0	23 (21.9)	35 (29.4)
−	14 (13.3)	13 (11)
Total	105 (100)	119 (100)

* See text for criteria.
† The numbers in parentheses are percentages.

TABLE III
ANALYSIS OF RESULTS IN TERMS OF SIZE OF ULCERS

Size of Ulcer	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
Small	5	2	7
Medium	27	5	32
Large	6	15	24
Extra-large	4	16	17
Total	42	38	80

TABLE IV
ANALYSIS OF RESULTS IN TERMS OF DEPTH OF ULCERS

Depth	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
Deep	36	38	74
Superficial	6	0	6
Total	42	38	80

TABLE V
ANALYSIS OF RESULTS IN TERMS OF DURATION OF ULCERS

Duration (yr.)	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
From 0 through 1	20	8	28
Over 1 through 5	9	11	20
Over 5 through 10	3	11	14
Over 10 through 20	8	8	16
Over 20	2	0	2
Total	42	38	80

TABLE VI
ANALYSIS OF RESULTS IN TERMS OF ETIOLOGY OF ULCERS

Etiology	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
Edema—trauma	23	22	45
Postphlebitic	42	16	35
Total	65	38	80

TABLE VII
ANALYSIS OF RESULTS IN TERMS OF HABITUS

Habitus	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
Obese	8	11	19
Normal	32	26	58
Thin	2	1	3
Total	42	38	80

women in the study, sixty-one of whom were Negro and nineteen were Caucasian.

In analyzing the results of therapy, courses rather than patients were considered since each patient received several courses of treatment, each with a different code number. It was found that in 65 per cent of the courses in which A5MP was administered, healing occurred to an extent equal to or greater than that anticipated from local care alone. In courses of therapy consisting of vehicle only, healing occurred to a comparable degree in 60 per cent. Similarly, about the same number of ulcers failed to show evidence of healing, or actually became worse during administration of A5MP and the vehicle alone. Thus, there was no significant difference in the healing of chronic ulcers of the leg treated with A5MP and those treated by the placebo. (Table II.)

Because of the possibility that certain variables might have influenced the results, an attempt was made to group the patients in such a way that these factors were largely eliminated. The results, therefore, were analyzed in terms of etiology, size, depth and duration of an ulcer, obesity, cooperation of the patient and extent to which a course of therapy was completed. (Tables III, IV, V, VI, VII, VIII and

TABLE VIII
ANALYSIS OF RESULTS IN TERMS OF LOCATION IN EACH LEG

Location	Right Leg			Left Leg		
	No. of Ulcers Healed	No. of Ulcers Unhealed	Total	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
Medial malleous	3	4	7	11	4	15
Lateral malleous	4	1	5	5	1	6
Medial shaft	1	0	1	3	3	6
Lateral shaft	0	1	1	1	1	2
Anterior shaft	1	3	4	7	0	7
Posterior shaft	2	0	2	0	2	2
Total	11	9	20	27	12	38

IX.) In no instance was there any indication that the administration of A5MP had favorably influenced the healing of chronic ulcers of the leg. Statistical analysis for the chi square method was applied to the data for the entire group and to the sub groups just described, but it was evident that in none of these was there a significant difference between the response to A5MP and to the placebo. The value for chi square in the entire group was less than .05, whereas it would have to be 2.7 or greater in order for any difference to be significant even at the 10 per cent level of probability.

Since exogenous adenosine-5-monophosphate had no influence upon the healing of ulcers of the leg under the conditions of this study, other factors were examined closely. One of these factors, which appeared to be of major importance, was the size and depth of a chronic ulcer. Thus, an ulcer of 100 sq. cm. in size, with no islands of epithelium in its base, required a longer interval for complete healing than an ulcer of the same area but with foci of epithelium remaining. Similarly, the large, full thickness ulcer required a longer time for healing than a small full thickness ulcer. In this series, the majority of ulcerations were medium in size and the largest percentage of healed ulcers was in this category. Thus, 82 per cent of the small and medium-sized ulcers healed completely during the course of the study but only 25 per cent of the large and extra-large ulcers healed. Nevertheless, at the termination of the study, nine of sixteen extra-large ulcerations while not completely healed were responding well to therapy. The importance of depth to healing of an ulcer is demonstrated by the fact that among seventy-four full thickness ulcers, less than a half healed completely, whereas all of the six superficial ulcers responded with complete healing.

The length of time an ulcer had been present was also found to influence the rate of healing. Among twenty-eight ulcers that had been present one year or less, 20 or 70 per cent healed during the course of the study. On the other hand, ulcerations existing for long periods of time did not respond well to therapy and only 40 per cent in this category healed completely.

As indicated earlier, the ulcers studied were of two etiologic types: traumatic and postphlebitic. In the former, an ulcer was the result of acute trauma superimposed upon edema of the extremity. The cause of the edema was not always clear and in some instances it may have

TABLE IX
ANALYSIS OF RESULTS IN TERMS OF NUMBER OF MONTHS OF THERAPY

No. of Months	No. of Ulcers Healed	No. of Ulcers Unhealed	Total
3	24	4	28
6	10	6	16
9	3	3	6
12	3	16	19
15	1	3	4
18	1	0	1
21	0	4	4
24	0	2	2
Total	42	38	80

been due to thrombophlebitis, although in none of the patients in this category could a history of this condition be elicited. Ulcers categorized as postphlebitic in origin clearly followed one or more episodes of thrombophlebitis. Comparison of the results for these two groups revealed that only one half of the ulcers caused by trauma healed completely, whereas about 75 per cent of postphlebitic ulcers healed.

It appeared that obesity might have had a bearing on the extent to which an ulcer healed under therapy. In this series, 42 per cent of ulcers occurring in obese individuals healed, and 55 per cent of those in individuals of normal weight or underweight healed completely. This difference is not as striking as one might expect in view of the fact that obese persons develop edema of the leg more readily than nonobese patients and tend to have more difficulty controlling swelling of the lower extremities.

Single ulcers occurred more frequently on the left leg than on the right leg and the results of therapy were better in this group. Among thirty-eight lesions on the left leg, healing occurred in twenty-seven or 70 per cent, but of twenty ulcers on the right leg, 55 per cent healed.

More than one half of the ulcers that healed did so within the first three months of therapy, and 80 per cent were healed within the first six months. Since each three month period represented a different therapeutic category, it is evident that response occurred as a result of adequate local care to the ulcer and that healing, when it occurred, was evident early in the course of treatment.

The importance of cooperation of the patient in maintaining cleanliness of the extremity and in proper application of compression bandages was emphasized by the experience with several patients whose ulcer healed during the first course of therapy. These patients then failed to report to the Clinic and did not wear the prescribed elastic stocking with the result that the ulcers redeveloped. Upon readmission to the study and resumption of proper care of the ulcer, healing commenced again.

Among ten patients with associated conditions which may have influenced healing, there were three with sicklemia; healing did not occur in two of the patients. There were two with traumatic ulcers superimposed upon old fractures of the lower extremity. Healing did not occur in either of these patients.

COMMENTS

This investigation of the effect of adenosine-5-monophosphate on the healing of chronic ulcers of the leg is unique, perhaps, in that it was conducted as a double blind study. In this way, any prejudice on the part of those conducting the investigation was eliminated. The conditions under which the study was carried out were standardized, insofar as possible, by adoption of a routine for local care of the ulcers and insistence that all patients be treated on an ambulatory basis. Under these conditions it was demonstrated that the administration of A5MP had no greater effect on healing of an ulcer than the administration of the vehicle alone. This is not to say that therapy was ineffectual but rather that local care of the ulcer was of primary importance.

It was observed that administration of A5MP or vehicle alike produced a sense of well-being in the recipients. In fact, this effect was so striking in some instances that patients were reluctant to have therapy discontinued. Others have attributed a mood-enhancing effect to A5MP [2,6] but this study suggests that if there is any specific psychologic action associated with administration of this material, it must be due to the phenol-gelatin vehicle rather than to A5MP, since the effects were noted in all categories of treatment.

The study has done nothing but confirm the fact that therapy of chronic nonspecific ulcers of the leg must include elimination or control of factors predisposing to ulceration. Although the exact mechanism for the development of these chronic lesions is not clearly understood, it is evident that incompetence of venous valves which follows thrombophlebitis, and lymphatic obstruction or other causes of peripheral edema are primary predisposing factors. Proper care of the ulcer itself plus measures which counteract the effects of venous incompetence and edema will result in the healing of a majority of chronic ulcers. On the other hand, these measures do nothing to permanently correct the underlying disorders and therefore treatment must be continued indefinitely. It is this discouraging aspect of the problem that causes a search for some agent which will bring about rapid epithelial covering of an ulcer, thus eliminating the need for prolonged and careful therapy by compression. The possibility is remote that such an agent will be found. In-

stead, efforts should be directed toward the development of methods for correcting the anatomic and physiologic abnormalities which lead to ulcer formation.

SUMMARY AND CONCLUSIONS

A double blind study was conducted on eighty patients over a two year period to determine if parenteral administration of adenosine-5-monophosphate would promote healing in ulcers of the leg. According to analysis of the data obtained during the course of this study, A5MP was found to have no significant effect on the healing of leg ulcers. Local care alone was primarily responsible for healing factors relating to the ulcer, and the quality and persistence of local care determined the rate and extent of healing.

ADDENDA

Patients from the vascular clinics of the Louisiana State University and independent services at Charity Hospital were included in this study with the kind permission of the chiefs of these services, Drs. J. D. Rives and Reichard Kahle.

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A Study of the Lethal Mechanism in Experimental Closed Loop Strangulated Obstruction of the Small Intestine

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The relative importance of the factors contributing to death following strangulated intestinal obstruction is obscure. As pointed out by Tanturi et al. [1], it is difficult to name any one factor leading to death after intestinal obstruction. Each case is different and the pathologic mechanisms change in importance. Extensive studies [2–4] have clearly demonstrated a major role of intestinal bacteria in death following strangulated obstruction. Much attention [5–7] has been devoted to the anaerobic organism, Clostridium perfringens, the producer of the potent exotoxin, lecithinase, as the possible principal lethal agent in strangulated obstruction. An important recent study by Katic et al. [8] indicates that the exotoxins of Cl. perfringens may enter the circulation by way of the intestines. They showed further that such toxins appear to augment the movement of bacterial cells through the intestinal mucosa into the blood. On the other hand, the bowel contains massive amounts of gram negative organisms such as Escherichia coli capable of producing the lipoplysaccharide endotoxins. These lipoplysaccharide substances are far less potent than the bacterial exotoxins: nevertheless they may play an important part in overwhelming the animals as they gain access to the peritoneal cavity.

A chemical and bacteriologic study of fluid collected at the time of death from the peritoneal cavities of dogs with strangulated closed loop obstruction of the lower ileum is presented herein. An examination of fluid was made for preformed toxic materials. The results indicate that viable enteric organisms must be present in the peritoneal fluid to cause rapid death.

METHODS

Closed loop obstruction with strangulation of the mesenteric vein was produced in segments of the lower ileum in dogs as described by Barnett et al. [9]. The animals died between nine and sixteen hours after the obstruction was produced. At the time of death the abdomen was opened, the dark red fluid aspirated from the peritoneal cavity and stored at 5°C. Perforation of the intestine was observed in all animals. The volume of fluid obtained from each animal ranged from 100 to 300 cc., depending upon the size of the animal.

1. *Determination of the Toxicity of the Supernatant and the Centrifugate of Strangulation Fluid.* At a force 15,500 times that of gravity 1 L. of pooled raw fluid obtained from several animals was subjected to centrifugation for fifteen minutes in a super centrifuge. The supernatant and the centrifugate were both retained. The centrifugate was washed five times with distilled water and recentrifuged after each washing at a force 15,500 times that of gravity for ten minutes. After the final washing, the centrifugate was suspended in a volume of saline solution equal to the original volume of fluid from which it was obtained. Immediately following this, aliquots of both the supernatant and the centrifugate were removed for bacteriologic study. The remainder of the two preparations was used in the following study on toxicity. A group of normal unanesthetized dogs received an intraperitoneal injection of

4 cc./kg. of body weight of the supernatant fluid. It has been shown by Barnett et al. [10] and confirmed by us that the minimum lethal dose of raw fluid is 3 cc./kg. of body weight. Another group of dogs received 4 cc./kg. of the washed centrifugate. Survival times were observed in both groups. This study was repeated in two groups of mice, using an intraperitoneal dose of 0.2 cc. of either fluid.

II. *Differential Centrifugation of Strangulation Fluid.* One hundred cc. of the raw fluid was divided into ten portions of 10 cc. and each placed in a plastic centrifuge tube. One tube was retained as a control. The remaining nine tubes were subjected to centrifugation for ten minutes. However, the relative centrifugal force was varied with each tube as shown in Table 1. Again the supernatant and the centrifugate were both retained and treated exactly as just described in the first procedure. The toxicity of these fractions was determined on normal mice by the intraperitoneal injection of 0.2 cc. of each supernatant and each centrifugate fraction. A similar study was performed with dogs.

III. *Examination of Strangulation Fluid for the Presence of Soluble Toxins.* Two hundred cc. of supernatant fluid obtained by centrifugation at a force 15,500 times that of gravity was subjected to Cohn's system of ethanol fractionation [11]. Each protein fraction obtained was lyophilized and redissolved in saline solution. The entire amount of each protein fraction was injected intraperitoneally into a dog to determine whether any protein concentrate of the supernatant fluid was toxic. A similar procedure was performed with ammonium sulfate fractionation [12] of 300 cc. of supernatant fluid. Whole peritoneal fluid and supernatant fluid were extracted three times with chloroform. The chloroform was removed by reduced pressure distillation at 20°C. All chloroform must be removed at this point since very small amounts will produce death in mice within a few minutes when given intraperitoneally.

IV. *Examination of Strangulation Fluid for the Presence of Endotoxins.* An attempt was made to demonstrate the presence of endotoxin by subjecting bacterial cells obtained from the peritoneal fluid to the following procedure: Peritoneal fluid was centrifuged at a force 15,500 times that of gravity for ten minutes. The supernatant was discarded. The centrifugate was washed three times with distilled water and recentrifuged each time. Enough distilled water was then added to produce a mixture that would pour easily. This mixture consisted of a suspension of bacteria and tissue debris. The temperature of the suspension was lowered to 3°C. and the suspension was poured slowly into approximately ten volumes of acetone with constant stirring. The temperature of the acetone before addition of the suspension was −20°C. This mixture was kept in the deep freeze at −20°C. until all particulate material had settled. The larger part of the acetone was decanted from the settled material. The remaining acetone was removed by centrifugation in a refrigerated centrifuge, followed by evaporation to dryness under a stream of dry nitrogen. The temperature was maintained at −20°C. during the drying process. The resulting dry residue was weighed and divided into equal parts, each part representing approximately the amount of centrifugate contained in 100 cc. of unaltered peritoneal fluid. One aliquot was suspended in 0.9 per cent saline solution and injected directly into a dog to establish lethality. In the remaining aliquots bacterial cells were lysed by the addition of 20 gm. of inactive Al_2O_3, followed by high speed homogenization for five minutes. (A small amount of antifoam was added prior to homogenization to prevent foaming.) The temperature was maintained at 3°C. during homogenization by means of an ice-salt bath.

TABLE 1
EFFECT OF DIFFERENTIAL CENTRIFUGATION OF PERITONEAL FLUID ON TWENTY-FOUR HOUR SURVIVAL IN MICE (0.2 CC./ANIMAL INTRAPERITONEALLY)

Relative Centrifugal Force	Supernatant		Centrifugate	
	Survived Twenty-Four Hr.	Died Twenty-Four Hr.	Survived Twenty-Four Hr.	Died Twenty-Four Hr.
65	0	9	3	6
130	0	9	0	9
500	0	9	0	9
1,200	9	0	0	0
2,000	9	0	0	9
3,200	9	0	0	9
4,600	9	0	0	9
6,300	9	0	0	9

TABLE II
STUDY OF THE TOXICITY OF VARIOUS FRACTIONS OBTAINED FROM THE CENTRIFUGATE OF PERITONEAL FLUID IN DOGS (INTRAPERITONEAL ADMINISTRATION)

Treatment of Centrifugate	No. Dogs Survived Twenty-Four Hr.	No. Dogs Died Twenty-Four Hr.
Unaltered Fluid*	0	2
Centrifugate of Fluid (15,500 × G)†	0	2
Acetone-dried Powder of Centrifugate‡	0	1
Lysed Cells Extracted with 5% NaCl	1	0
Lysed Cells Extracted with 2% TCA	1	0
Lysed Cells Extracted with 1% Na Citrate	1	0
Lysed Cells Extracted with 0.01 N Na Carbonate	1	0
Lysed Cells Extracted with 0.1 M HAc	1	0

* Peritoneal fluid from which centrifugate was obtained.

† The fractions listed below were all obtained from this centrifugate.

‡ Large numbers of viable aerobic bacteria were present in this preparation.

After homogenization each of the remaining aliquots was extracted with a different agent as indicated in Table II. The samples were allowed to extract at 3°C. for forty-eight hours after which they were centrifuged at a force 15,500 times that of gravity. The supernatant from each sample was poured into ten volumes of acetone at −20°C. as described previously and the resulting precipitate dried by nitrogen in the cold. To each of the dry residues 100 cc. of distilled water was added and allowed to dialyze against large volumes of distilled water at 3°C. for seventy-two hours. After dialysis, the total volume of each sample was reduced to approximately 30 cc. by prevaporation at 3°C. and NaCl added to achieve isotonicity. The toxicity of each fraction was determined by the intraperitoneal injection of each entire fraction into dogs.

v. *Circulatory Contamination by Aerobic Bacteria after Intraperitoneal Injection of Strangulation Fluid.* The following study was designed to determine whether viable bacteria present in the strangulation fluid pass into the circulation after intraperitoneal injection. Healthy adult dogs were anesthetized with pentobarbital. A midline abdominal incision was made and a tributary of the portal vein (splenic vein) was cannulated with a sterile polyethylene cannula. One end of the cannula was brought to the outside and the abdomen closed. Similarly, the left femoral vein was exposed and cannulated. All surgical and cannulation procedures were performed with careful aseptic technic.

Control blood samples were obtained aseptically from both the portal and femoral veins of sixteen dogs. Thirteen of these animals then received 4 cc./kg. of unaltered strangulation fluid intraperitoneally. Three control dogs were cannulated but received only sterile saline solution intraperitoneally. Additional blood samples were collected aseptically from the experimental animals thirty minutes, one and a half, two and a half and four hours after injection. Samples were obtained from the three control animals at the same time intervals.

Immediately after each blood sample was drawn, an aliquot of 1 cc. of undiluted whole blood was spread directly onto the surface of trypticase soy agar media in a Petri dish. Duplicate plates were prepared for each sample. The cultures were incubated at 37°C. for twenty-four hours, after which the bacterial colonies were counted.

vi. *Incubation of the Supernatant Strangulation Fluid.* Two hundred cc. of unaltered strangulation fluid was centrifuged as previously described. The supernatant was divided into two equal portions and one portion stored at 3°C. The other portion was incubated at 37°C. for twenty-four hours. At the end of the twenty-four hour period, 0.2 cc. of the incubated supernatant was given intraperitoneally to thirty mice. Similarly, 0.2 cc. of the refrigerated supernatant was injected into thirty mice. Survival times of both groups were observed.

vii. *Attempts to Protect against the Lethal Effect of Strangulation Fluid by Immunization.* An experiment not reported in detail herein definitely indicated that animals could be completely protected from a minimum lethal dose of the toxic fluid by several intraperitoneal injections of small amounts of unaltered strangulation fluid. Thus, an attempt was made to determine whether viable bacterial cells play a role in this observed protection. Four strains of bacteria including proteus, a coagu-

TABLE III
TWENTY-FOUR HOUR SURVIVAL STUDY OF SUPERNATANT AND CENTRIFUGATE OF PERITONEAL FLUID IN DOGS AND MICE (RELATIVE CENTRIFUGAL FORCE OF 15,500)

Animal	Dose	Supernatant		Centrifugate	
		Survived Twenty-Four Hr.	Died Twenty-Four Hr.	Survived Twenty-Four Hr.	Died Twenty-Four Hr.
Dogs....	4 cc./kg.	10	0	0	10
Mice....	0.2 cc.	10	0	1	16

TABLE IV
EFFECT OF DIFFERENTIAL CENTRIFUGATION OF PERITONEAL FLUID ON TWENTY-FOUR HOUR SURVIVAL IN DOGS (4 CC./KG. BODY WEIGHT)

Relative Centrifugal Force	Supernatant		Centrifugate	
	Survived Twenty-Four Hr.	Died Twenty-Four Hr.	Survived Twenty-Four Hr.	Died Twenty-Four Hr.
300	0	3	0	3
25,000	5	1	0	5

lase-positive and a coagulase-negative staphylococcus, and E. coli were arbitrarily isolated from pooled unaltered peritoneal fluid from several animals with strangulated obstruction.

Pure cultures of each of these four microorganisms were stored at 4°c. Each week for three weeks fresh cultures were prepared from these stock cultures. The fresh cultures were allowed to incubate at 37°c. for twenty-four hours after which the cells were suspended in 10 cc. of saline solution. Each week for three weeks 0.2 ml. of the saline suspension of each type of bacteria was injected intraperitoneally into two dogs. The number of bacterial cells injected in each case was in the order of 10^7 cells. Four days after the last injection of bacterial suspension, all dogs were injected with 3 cc./kg. of body weight of the unaltered fluid and the survival times observed.

RESULTS

I. *Toxicity of the Supernatant and the Centrifugate.* Data presented in Table III established that the lethal factor contained in strangulation fluid is removed from the fluid by centrifugation. In this study two of twelve mice died after receiving intraperitoneal injections of supernatant fluid in an amount equivalent to a lethal dose of unaltered fluid. All except one animal that received intraperitoneal injections of an equivalent amount of the centrifugate died within twenty-four hours. The toxic factor, therefore, appears to be either an insoluble material or almost completely adsorbed to the tissue debris or bacterial cells of which the centrifugate is composed. Microscopic examination of the centrifugate revealed large numbers of gram positive and gram negative microorganisms. Standard plate counts showed the number of aerobic microorganisms to be on the order of 10^7 cells/cc. of centrifugate. Aliquots for counting were obtained after the centrifugate had been resuspended in a volume of 0.9 per cent sterile saline solution equal to the volume of fluid from which the centrifugate was obtained. Although anaerobic organisms were not counted, they were shown to be present in large numbers by anerobic culture of the centrifugate. The supernatant still contained microorganisms after fifteen minutes of centrifugation at a force 15,500 times that of gravity as demonstrated by plate counts.

II. *Differential Centrifugation.* Table I gives the results of survival studies in mice after differential centrifugation of strangulation fluid. It is evident that the toxic factor is removed by very low centrifugal forces and reaches nontoxic levels in the supernatant at a relative centrifugal force of 1,200. These results were confirmed in dogs. (Table IV.)

III. *Soluble Toxins.* No protein fraction obtained by ethanol or ammonium sulfate fractionation produced any ill effects after intraperitoneal injection into dogs. Similarly, the chloroform extractable material exhibited no toxicity in dogs or mice. The negative nature of this particular experiment decreases the possibility of the presence of a bacterial exotoxin in amounts sufficient to produce death.

IV. *Endotoxins.* Table II summarizes the attempt to demonstrate bacterial endotoxins in the centrifugate of strangulation fluid. Although no endotoxin could be demonstrated these data do not definitely establish the absence of such a substance. Very large numbers of viable bacterial cells were demonstrated in the acetone dried centrifugate. Although death resulted from injection of this aliquot, one cannot conclude that the cause of death

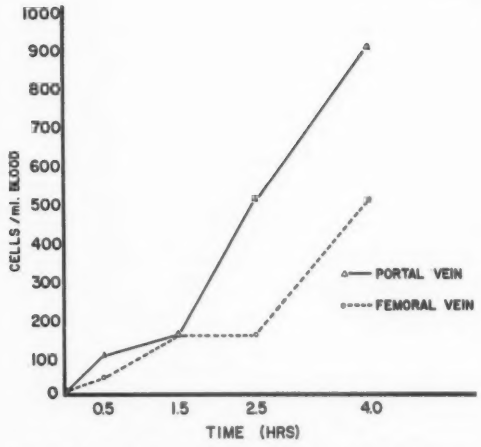

FIG. 1. Mean appearance curves of aerobic microorganisms in portal and femoral venous blood after intraperitoneal injection of strangulation fluid (4 cc./kg.) in eleven dogs. The fluid injected was obtained from dogs which died from a closed loop strangulated obstruction.

was due to endotoxins because of the presence of viable microorganisms.

v. *Circulatory Invasion by Bacteria.* Figure 1 shows the mean rate of appearance of aerobic microorganisms into the circulation after intraperitoneal administration. It is not clear how the bacterial cells enter the portal circulation at a rate greater than that observed in the femoral vein. It is noteworthy that only two types of microorganisms were demonstrated in the circulation. E. coli was found in eight of the eleven dogs and streptococci in three. All control blood samples obtained from the eleven dogs that received the peritoneal fluid were free of aerobic organisms. Similarly, the three control dogs exhibited no bacterial contamination of portal or femoral venous blood.

vi. *Incubated Supernatant Fluid.* Supernatant fluid stored at 3°c. for twenty-four hours when given intraperitoneally to mice resulted in the death of five of the thirty animals within twenty-four hours. (Table v.) On the other hand, the same supernatant fluid after a twenty-four hour incubation produced death in twenty-six of the thirty animals within twenty-four hours after administration. These data clearly show that the toxicity of the centrifuged supernatant fluid is restored by incubation. It is important to note that within 120 hours after administration twenty-three of the thirty mice receiving the refrigerated supernatant fluid died. Such greatly prolonged survival times are not observed in animals receiving unaltered fluid or the centrifugate of strangulation fluid unless the administered dose is decreased to very low levels.

vii. *Immunization Studies.* The survival times of dogs given lethal amounts of peritoneal fluid after attempts at immunization are given in Table vi. Two dogs that received the injection of E. coli survived twelve and thirty-six hours, respectively, which was longer than the remainder of the animals. Although this difference in survival times is unusual in our experience, the significance of this experiment must await evaluation until these and other organisms have been tested on a large series of animals.

TABLE V

SURVIVAL STUDY IN MICE RECEIVING INCUBATED OR REFRIGERATED SUPERNATANT FLUID (0.2 CC./ANIMAL INTRAPERITONEALLY)

Hours after Injection	Refrigerated Supernatant*		Incubated Supernatant*	
	No. Survived	No. Died	No. Survived	No. Died
24	25	5	4	26
48	19	6	0	...
72	19	6	...	...
96	8	11	...	...
120	7	1	...	...

* Total of thirty mice in each group.

COMMENTS

Nemir et al. [13] and more recently Barnett and Hardy [10] have demonstrated that in

TABLE VI

SURVIVAL TIMES IN DOGS CHALLENGED WITH LETHAL AMOUNTS (3 CC./KG.) OF PERITONEAL FLUID ONE WEEK AFTER RECEIVING INTRAPERITONEAL INJECTIONS OF PURE BACTERIAL CULTURES

Dog No.	Microorganism Injected	Survival Time (hr.) after Challenge with Toxic Fluid
661	Proteus	12
662	Proteus	12
671	Coagulase-positive staphylococcus	12
672	Coagulase-positive staphylococcus	12
681	Coagulase-negative staphylococcus	12
682	Coagulase-negative staphylococcus	Died before injection
691	E. coli	24
692	E. coli	48

normal dogs the degree of toxicity of late strangulation fluid obtained from the peritoneal cavities of various dogs does not vary greatly. Barnett and Hardy [*10*] were able roughly to establish a minimum lethal dose for twenty-four hours in dogs. This dose of later peritoneal fluid was found to be 3 cc./kg. of body weight when given intraperitoneally. We have confirmed this finding.

In the chemical studies of peritoneal fluid reported herein, all isolated fractions were obtained from an amount of late peritoneal fluid equivalent to at least five lethal doses in any animal injected. Although anaerobic culture of raw fluid showed the presence of clostridia, isolation procedures in this study demonstrated no significant amounts of clostridium exotoxins. The alpha toxin of Cl. perfringens should have been revealed in the ammonium sulfate fractionation procedure [*14*] but we were unable to demonstrate it in the survival studies reported herein. Other investigators, however, have demonstrated the presence of alpha toxin [*6,7*] in strangulation fluid by the use of more sensitive technics.

Although we found no evidence of lethal amounts of soluble exotoxins in the peritoneal fluid, some investigators think that gas gangrene antitoxin is of benefit in the treatment of intestinal obstruction and peritonitis [*7*].

Since the toxic fluid can be rendered relatively innocuous by low centrifugal forces and isolation procedures demonstrated no lethal amounts of exotoxins, it is unlikely that a soluble material is responsible for rapid death unless it resides within the bacterial bodies or is completely adsorbed to tissue debris.

The nontoxic nature of the supernatant obtained after centrifugation was not surprising since Murphy et al. [*15*] in 1915 found that an ultrafiltrate of fluid from closed loops was nontoxic whereas before filtration it was highly toxic.

The presence of lethal amounts of adsorbed toxins is unlikely since no such material could be demonstrated in the present study following homogenization of fluid centrifugates and extraction with the solvents given in Table II. Furthermore, when nontoxic supernatant fluid is incubated for twenty-four hours, the toxicity of the supernatant is fully restored. During this incubation time the bacterial count of the incubated supernatant fluid rises to levels found in noncentrifuged fluid. This indicates, although not conclusively, that toxicity of the fluid may fluctuate with bacterial count. Dragstedt et al. [*16*] demonstrated earlier that bacteria were necessary for development of the toxicity of peritoneal fluid. The major role of bacteria is further emphasized by the work of Dragstedt et al. [*17*] and Cohn and Hawthorne [*18*], who showed that sterile intestinal segments could be placed in the peritoneal cavity of dogs without harm to the animals. This work clearly indicates that autolytic products are not toxic.

Since it appears that the toxicity of peritoneal fluid from late strangulated obstruction depends upon the presence of bacteria, the question arises as to whether the bacterial cells must be viable.

In the present study the centrifugate of the fluid was subjected to homogenization procedures that result in about 90 per cent lysis of bacterial cells. The centrifugate contains by far the bulk of the bacterial cells of the fluid. However, no evidence of a lethal substance could be demonstrated after cellular lysis, indicating that significant amounts of bacterial endotoxins are not present in strangulation fluid.

Another finding which tends to eliminate preformed toxic substances as a major cause of death from strangulated obstruction is that toxicity of the centrifugate can be decreased markedly by subjection to ultrasonics for eighty minutes or by exposure to a temperature of 58°C. for one hour. Each of these treatments results in a decreased bacterial count. When the toxic fluid is heated at 58°C. for one hour and then given to dogs, they survive an amount of fluid equal to twice the lethal dose of unheated fluid. The aerobic bacterial count before heating is usually on the order of 10^7 viable cells/cc. of fluid, and after heating the count decreases to the order of 10^4 cells/cc. Here again is evidence that decreasing the number of viable cells produces a concomitant decrease in toxicity of the fluid.

It was emphasized at the beginning of this work that the peritoneal fluid was obtained after gross perforation of the bowel had occurred. The fluid was taken at this stage since Calihan et al. [*19*] showed, from a large series of cases of acute mechanical obstruction, that 55 per cent of the deaths were due to peritonitis produced probably as a result of bowel perforation to some degree. Harper et al. [*20*] pointed out that as the bowel is distended, the wall

becomes ischemic and thus susceptible to bacterial attack, the wall rapidly proceeds to ulcerate and bacterial necrosis begins. Distention of the intestinal wall is a factor which allows bacteria to attack the wall, as pointed out earlier by Harper and Blain [*21*]. These authors showed that penicillin placed in closed loops would effectively protect the wall of the bowel from bacterial attack. The deterimental role of distention was probably first indicated by the experiments of Murphy and Brooks [*15*] in 1915.

In the present work it was showed that after injection of strangulation fluid into the peritoneal cavity of normal dogs, viable bacteria rapidly enter the circulation. The passage of bacteria across the peritoneal barrier was noted by Durham [*22*] and Simoneini [*23*] in 1897 and confirmed by later investigators [*24–26*]. The absorption of particulate matter from the peritoneal cavity has been known to occur for many years [*27*]. However, Nemir et al. [*28*], in a careful study of moribund dogs suffering from strangulation obstruction, found positive blood cultures in only two of seven animals. In the present study, all eleven dogs receiving intraperitoneal injections of strangulation fluid had positive blood cultures within thirty minutes after injection. At the same time, three sham-operated control animals that received injections of sterile saline solution exhibited negative blood cultures. Therefore, it appears that soon after the bowel perforates following an obstruction viable bacteria enter the circulation. The route of entry is probably by way of the lymphatics [*22*].

Although E. coli was the organism most commonly found in the blood of dogs receiving intraperitoneal injections of strangulation fluid, a strain of streptococci was observed in three animals. It is known that certain streptococci contain the toxin, leucocidin, as well as certain hemolysins [*29*]. Therefore, the invasion of such organisms into the circulation at the time of perforation might partly explain the rapid fall in white blood cell count, as observed by Barnett et al. [*30*] after administration of strangulation fluid.

A number of studies [*21,31–33*] have shown that antibiotics are effective in prolonging the survival time of animals suffering from strangulated obstruction. One of the more striking studies is the recent work of Barnett et al. [*34*] who administered massive doses of antibiotics intraperitoneally into dogs with strangulated obstruction. The efficacy of antibiotic therapy further supports the hypothesis that viable bacteria are a major factor in death resulting from strangulated obstruction. The work of Schweinberg et al. [*35*] in experimental peritonitis also leads support to such a view.

It has long been known that the tolerance of animals to highly toxic intestinal contents can be greatly increased by subsequent small intraperitoneal injections of the bowel contents several days before a challenging dose [*36–38*]. We found that the tolerance of mice and rats to strangulation fluid obtained from dogs can be increased in a similar manner to a point at which they can sustain lethal doses of the fluid without ill effect. This would argue for a viable bacterial mechanism playing a role in death from strangulated obstruction. On the other hand, increases of tolerance to pure endotoxins also occur [*39*]. If death from strangulated obstruction is indeed due to endotoxins, the difficult problem is to determine whether death is due to preformed toxins or those formed systemically after the bacterial organisms have entered the circulation. The present study stresses the importance of viable bacterial cells and argues against but does not preclude any important role that might be played by preformed toxins in the strangulation death. If lethal amounts of bacterial toxins were already present it is difficult to see how antibiotics would protect; yet it is known that they do offer a high degree of protection against lethal quantities of strangulation fluid.

SUMMARY

The toxicity of peritoneal fluid obtained from dogs which died from a strangulated obstruction of the lower ileum can be greatly decreased by centrifugation at relatively low forces. The bulk of the toxic material is present in the centrifugate. Examination of the supernatant and the centrifugate of peritoneal fluid for bacterial exotoxins and endotoxins and subsequent survival studies in healthy dogs and mice given the isolated fractions indicated that insufficient amounts of such materials were present to cause death. Evidence was obtained for the rapid circulatory invasion of aerobic bacteria after the intraperitoneal injection of peritoneal fluid into healthy dogs. However, all peritoneal fluid used in this study was collected after gross perforation of the bowel. Two or-

ganisms, E. coli and a beta hemolytic streptococcus, were identified in the blood of dogs receiving intraperitoneal injections of the fluid. Anaerobic organisms were not studied. Tolerance to the fluid could be greatly increased in dogs and mice by giving small amounts of the fluid intraperitoneally several days before the challenging dose. On the other hand, no protection from the fluid was observed when four different pure bacterial cultures were given.

Procedures tending to diminish the number of viable bacterial cells resulted in a decrease in the toxicity of peritoneal fluid. Such procedures included centrifugation, ultrasonic exposure and heat. The toxicity of supernatant fluid obtained by centrifugation is restored by twenty-four hour incubation. This study strongly indicates that the toxicity of peritoneal fluid fluctuates with the number of viable bacterial cells present.

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A Severe Wringer Injury with Osseous Involvement

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THIS paper presents a case of wringer injury with involvement of the radius and a discussion of the possible cause. Since the article by MacCollum [1] in 1938, many cases have been described which were associated with fracture. In 1955 Entin [2] reviewed the work of seven authors totaling 559 cases, and reported a total of thirteen associated fractures. Adams and Fowler [3] reported four fractures in 120 cases, and MacCollum et al. [4] in 1952 reported four fractures in 116 cases.

This total of 795 cases included twenty-one fractures or 2.6 per cent. Three of these were reported by Schulz [5] and were considered pathologic fractures. In a recent personal communication [6], Schulz stated that two of the patients required bone graft. The damage was apparent immediately after the injury. A survey of the literature fails to reveal any reports of delayed osseous involvement as demonstrated in the case reported herein.

Wringer injuries vary in degree from minimal edematous changes to complete loss of a part or extremity. The essential rule in the management of a wringer injury, after emergency care, is careful observation of the involved part until the initial reaction has subsided and the degree of injury can be evaluated. The possibility of fracture is always considered but rarely occurs. When it does occur, it is generally the result of extracting the involved part from the wringer.

CASE REPORT

A three year old white girl was seen nine days after a wringer injury that produced a large, oval shaped wound of the anterior forearm. Initial care consisted of sterile dressings. At the time of admission, extensive soft tissue necrosis was apparent. (Fig. 1A.) However, early, complete debridement was not performed due to an inability to determine the extent of involvement. The median nerve was avulsed approximately 3 inches, and palsy of the radial nerve was evident. A small segment of radius was exposed by surgical debridement twenty-three days following injury. The bone appeared viable and granulations rapidly covered the area. Necrosis of the soft tissue included the flexor digitorum sublimis tendons, but not those of the flexor digitorum profundus.

The debrided wound granulated rapidly and seven days later a split-thickness graft was applied. The patient was discharged with the wound healed. Eighty-five days after the injury the patient returned for definitive flap coverage. There was contracture of the split-thickness graft and flexion contracture of the fingers due to tendon adhesions and contractures. (Fig. 1B.) A roentgenogram was taken routinely, but was not seen prior to attachment of the flap.

The graft and deep scar were excised. The flexor digitorum sublimis tendons were transected and freed from the scar attachment. The flexor digitorum profundus was intact. This release allowed the hand and fingers to extend normally. A lower thoracic pattern-type [7] abdominal flap was attached to the forearm. The flap was detached in two stages. (Fig. 1C.)

The initial roentgenogram of the forearm had shown no evidence of bony injury. A routine film had been ordered fifty-four days after injury (Fig. 2) when there was no clinical suspicion of bony

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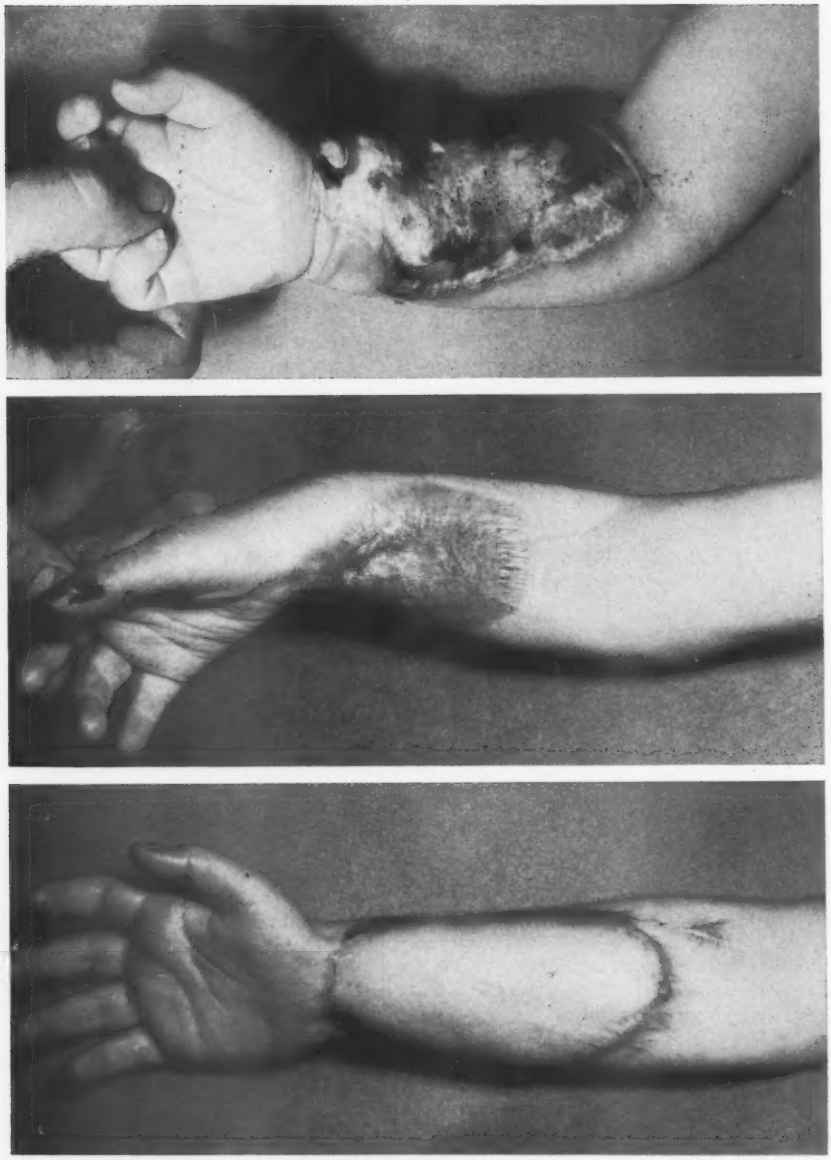

FIG. 1. A, extent of damage to the anterior forearm ten days after injury. B, status of forearm eighty-five days after injury. Note the angulation and contracture. C, the arm with the flap intact. Angulation has improved.

damage. This showed only periosteal reaction at the distal ulna. The radiologist suggested progress films to determine whether this was due to trauma or possibly osteomyelitis.

Eighty-five days following injury (Fig. 3), roentgenogram showed a "moth eaten" appearance of the distal radius. On lateral view a sclerotic area was observed which was described as a "sequestrum." The distal fragment was volarly angulated which was believed to be due to osteomyelitis. At this time the flap was attached and the forearm immobilized. One hundred thirty-four days after

FIG. 2. A and B, roentgenograms of the forearm fifty-four days after injury. There is slight periosteal new bone formation in the distal radius and ulna (B).

FIG. 3. Roentgenograms of the forearm eighty-five days after injury. A, the volar side of the radius shows a semilunar-shaped sclerotic area of bone about 1 cm. long and 3 to 4 mm. wide separated from the normal bone by a ring of demineralization. B, there has been about 20 degrees of volar angulation of the distal radius.

FIG. 4. Roentgenograms of the forearm 173 days after injury. A, the previously described area has been replaced by new bone. The bone is clinically solid. B, volar angulation is less. There is considerable thickening of the ulna from periosteal new bone formation.

injury, the sclerotic area had disappeared and there was slight improvement in mineralization at the site of the bony lesion. There was increase in bone formation around the ulna. By six months after injury, the bone was solidly healed on roentgenogram. (Fig. 4.)

Presently the anterior forearm flap is well healed. There is no bony disease. Except for the loss of function of the median nerve, the hand is satisfactory.

COMMENTS

We have used the term "bony involvement" in referring to the roentgenogram of the lesion. The roentgenogram most nearly resembles the roentgenographic changes of osseous necrosis. The term necrosis has not been used as we did not have histologic evidence of death of osteocytes. However, since osseous necrosis would produce roentgenographic changes similar to those seen in this case, and any other conditions producing sclerotic changes surrounded by demineralization are very unlikely, the term necrosis will be used to describe this bony involvement.

At no time during the child's course was there any clinical suggestion of osteomyelitis. She remained completely afebrile. The split-thickness grafts and flap healed uneventfully. There was no swelling, redness or drainage. It was not until two months after the application of the skin graft that the osseous necrosis was observed on roentgenogram. Although

the superficial contamination was evident, we believe that infection played no part in the pathogenesis of the bony necrosis.

We have attempted to determine the cause of this osseous necrosis. Osteomyelitis was not present, and the necrosis followed a severe injury. It can be called an aseptic necrosis, but this does not explain the pathogenesis. Weinmann and Sicher [*8*] state that trauma leads to necrosis of bone if it destroys or greatly restricts the blood supply to the bone. The new bone formation in our case showed that the periosteum had been disturbed by the injury. However, the periosteum may be surgically elevated over a large portion of a bone without the development of avascular necrosis. It is generally accepted that the outer part of the cortex is supplied by the periosteal vessels and the inner part of the cortex and the medulla by the nutrient artery. However, recent studies by Nelson et al. [*9*] have shown that a rich anastomosis exists between these vessels. We believe that in the case reported herein, vascular impairment had not been adequate to produce these changes.

Pressure as a cause of necrosis must be considered in this case. We know that pressure may cause resorption of bone. Pressure applied between the wringers will exert an equal force on both sides of the arm; yet, in typical wringer injury, as is the present case, necrosis of soft tissue occurs only on one side of the arm. Therefore, we do not believe that pressure was responsible for the bony necrosis in our case.

In the usual wringer washing machine, only one roller is powered, the other is passive. When the arm is caught in the wringer, the powered roller continues to turn and heat is generated by the friction. This explains why the soft tissue necrosis occurs only on one side of the arm. In our case, the osseous necrosis occurred only in the area of bone directly under the area of soft tissue necrosis. We believe that heat is the most likely cause of osseous necrosis.

The medical literature on thermal injuries of bone is inadequate. Weinmann and Sicher [*10*] state that in gangrene of an extremity from burning or freezing, the involved skeletal parts are necrotic and are separated from the intact bone by osteoclasis and proliferation of granulation tissue. The roentgenogram in our case fits this description.

CONCLUSION

Osseous necrosis may occur following a wringer injury. If clinicians are aware of this possibility occurring ten to twelve weeks after injury, we believe that many other cases will be observed.

The most reasonable explanation of the pathogenesis of the osseous necrosis is that it is due to the heat generated by the friction of the turning wringer. The condition is self-limited. No treatment is required other than immobilization to protect against deformity which might occur as a result of pathologic fracture. This must not be confused with extensive injuries which cause exposure of large bony surfaces. There is need for an experimental study on traumatic necrosis of bone.

SUMMARY

A case is presented of a wringer injury of the forearm which was complicated by osseous necrosis. The literature on wringer injuries is reviewed in regard to the skeletal complications of this type of injury. The probable pathogenesis of the osseous necrosis is discussed.

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Diagnosis of Torn Meniscus

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TODAY, injuries to the knee are an important cause of loss of manpower, from the standpoint of both prolonged convalescence and permanent partial disability. Many derangements are correctable by surgical intervention, but a good number of patients do not benefit from arthrotomy. On the contrary, the added strain of surgery further insults an already inadequate quadriceps muscle and the patient is left with more disability than he had at the outset.

DuToit states that if the end result of a meniscectomy is not satisfactory, the reason has to be sought by further careful examination with subsequent revision of the diagnosis.‡ If this revision could be achieved without recourse to arthrotomy, many patients would be spared an unnecessary operation. However, at the other end of the gamut, indecision and late surgery allow the development of arthritis, synovitis and atrophy of the quadriceps.

The decision to operate should be based on careful examination of the history and the results of physical examination and x-ray studies. Of these, the most important is careful examination of the history. The physical findings of tenderness, effusion, locking, the presence of a click and wasting of the quadriceps are the standard abnormal findings in internal derangements of the knee joint. The purpose of this study is to evaluate their relative value.

METHODS AND MATERIALS

Selected for this study were fifty-seven consecutive patients with a diagnosis of internal derangement of the knee joint on whom an arthrotomy was performed between 1954 and 1957 at the U. S. Naval Hospital in Newport, Rhode Island. Fifty-four of the group were in the third decade of life.

A history of injury was elicited for thirty-six patients. (Table 1.) The majority of these injuries were produced by twisting or falling at work or during an automobile accident. The percentages paralleled those of Smellie in England.§ However, it would seem that the British football player was twice as susceptible to injuries to the knee as his United States counterpart. Automobile accidents account for more injuries in this country. (Table 1.)

TABLE 1
HISTORY OF INJURIES TO THE KNEE

Cause of Injury	No. of Patients*	No. of Patients with Torn Meniscus	Smellie Series (%)
Coal mining and industry	0 (0)	0	24
Football	10 (18)	4	38
Other sports	5 (9)	0	12
Other types of work and automobile accidents	21 (36)	6	14
No history of an injury	21 (36)	5	12
Total	57	15	100

* Numbers in parentheses represent per cent of series.

Of the twenty-one patients (36 per cent) from whom no history of injury was elicited, surgery verified that five had a torn meniscus. Smellie, in a larger series, noted the absence of

‡ DUTOIT, G. T. Internal Derangement of the Knee Joints. American Academy of Orthopedic Surgeons Instructional Course Lecture, vol. 12, p. 9, 1955.

§ SMELLIE, I. S. Injuries of the Knee Joint. Edinburgh, 1951. E. & S. Livingstone, Ltd.

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† Present address: 101 West 111th Street, Chicago, Illinois.

TABLE II
PATHOLOGICAL FINDINGS CORRELATED WITH HISTORY OF INJURY

Pathologic Findings	No. of Patients	No. of Patients with History of Injury
Torn menisci	15	10
Fractured patellae	3	3
Osteochondritis	...	...
Chondromalacia	27	17
Acute synovitis	3	2
Cyst of menisci	3	2
Normal knee joint	6	2

the history of injury for 12 per cent of the patients who had a meniscectomy for a torn cartilage.

The duration of symptoms varied from one week to more than five years. The history of an injury to the knee for less than half the group was less than one year. One third of the patients who had a torn meniscus did not give a definite history of injury, whereas two out of three who had acute synovitis and seventeen of twenty-seven who had osteochondritis dissecans and/or chondromalacia had antecedent trauma. (Table II.) Further confusion is added by a clear-cut history of injury for one third of the patients who had normal articular surfaces at surgery. Sport and activities unrelated to duty were the causative factors for more than half of the injuries in both series.

SYMPTOMS

Tenderness. Tenderness was almost invariably present, and in half of our patients it was elicited on the lateral as well as the medial aspect of the knee joint. The most common site was the anterior peripheral attachment of the medial semilunar cartilage, but occasionally tenderness was generalized throughout the joint surface. Tenderness upon patellar tap in the presence of an effusion was usually indicative of osteochondritis.

While the absence of tenderness does not negate the diagnosis, it is a good reason for discretion. In one patient, who had a history of pain in the joint and locking but who did not experience tenderness, the knee was found to be entirely normal on exploration.

Effusion. If associated with a history of injury, effusion is probably the most definite sign of internal derangement of the knee joint. In our series, an effusion was present in thirty-eight patients, and in only two of these was the knee considered normal at surgery.

TABLE III
POSITIVE FINDINGS IN PATIENTS WITH NORMAL KNEE JOINTS

Positive Findings	Patients with Normal Knees (%)
History of injury	33⅓
Presence of effusion	5
History of locking	20
Presence of a click	17

Locking. A history of locking of the knee joint was present in ten of fifty-seven patients. Of the ten, five had a ruptured meniscus, three had osteochondritis dissecans with cartilaginous loose bodies and two showed no evidence of an abnormality. In the latter the meniscus was left intact; there were no postoperative complications.

Thus, 20 per cent were false positive results for locking of the knee joint. Only five of the fifteen patients with a torn meniscus gave a history of locking. In Smellie's series of 400 cases of arthrotomies for ruptured meniscus, 52 per cent of the patients had no history of locking. He emphasized that locking is no longer the *sine qua non* of our diagnosis of ruptured meniscus.

Presence of a Click. This finding was present in seventeen of the fifty-seven patients. Three of these had normal knees on exploration. Four of the remaining fourteen patients who had pathologic knees, had a torn meniscus. We concluded that a unilateral click was of definite diagnostic value; if, however, a similar symptom was present in the opposite knee one should proceed with caution.

Wasting of the Quadriceps. This was noted in all patients whose symptoms were of more than one week's duration. The degree of wasting varied from 1 to 5 cm. as measured at the midthigh. It is important to realize that flattening of the quadriceps is indicative of wasting and is visible before a difference in mensuration can be obtained.

Locking occurred in 20 per cent and a click was present in 17 per cent of the patients whose knees proved to be normal at surgery. (Table III.) We believe that these findings *per se* are not sufficient ground for the removal of a meniscus which looks normal during surgery.

TABLE IV
ABSENCE OF SYMPTOMS IN PATIENTS WITH PATHOLOGIC KNEE JOINTS

Symptoms Absent	Our Series (%)	Smellie (%)
History of injury	33	12
History of locking	66	52
A click	30	...
Error in diagnosis	15	6

NOTE: In our series there was an error in diagnosis of 15 per cent, and 6 per cent in Smellie's series.

Many of the classic symptoms can be absent in a given patient, but surgery should not be delayed unduly because the patient does not have all of the standard symptoms. In our series the preoperative hospital stay varied from one to 120 days, with an average of fourteen days.

In Table IV, the absence of some of the classic symptoms is correlated with the presence of abnormalities in the knee joint. The absence of locking in pathologic knees was the most striking. Our percentages parallel closely with those of Smellie.

DIAGNOSIS

We relied solely on the standard anteroposterior lateral, tunnel, and tangential projections without recourse to arthrography. While roentgenograms are of positive diagnostic value in about one-fourth of the patients, it must be borne in mind that false negative results are more frequent. In none of our patients on whom a menisectomy was performed was there narrowing of the space in the joint.

The radiographs of fifty patients were reviewed. Positive findings were encountered in sixteen; eight showed evidence of osteochondritis dissecans. There were two cases of osteochondromatosis; one of these patients also had Pellegrini-Steida disease. There was one other instance of this condition. One patient who had had a meniscectomy previously showed spurring of the condyles and presence of a joint mouse (osteocartilaginous loose body). The pathologic diagnosis in this case was osteochondroma. There were three patients with fractured patellae. Another showed spurring of the tibial plateau; an arthrotomy was performed and the medial meniscus removed and found to be intact. However, excessive synovial fluid and loose fragments of cartilage were found in the space in the joint. Of the fifteen patients with a torn meniscus, thirteen had normal radiographs. Normal radiographs were also obtained for two patients who had had a meniscectomy previously. A third showed spurring of the medial tibial plateau. However, the space in the joint in all patients was symmetrical.

In patients with a ruptured meniscus, elongation of the corresponding articular edge of the lateral border of the tibia has been described. This was noted in only one patient in our study.

It is of value to obtain roentgenograms of the asymptomatic knee of all patients; asymmetry of the space in the joint has been interpreted as indicating a rupture of the meniscus. Under normal circumstances the medial and lateral aspects of the knee joint may differ; the finding is only of diagnostic value when a comparison with the opposite knee shows a discrepancy. In only two of our patients was there asymmetry: one was a case of osteoarthritis, the other a case of loose bodies in the space in the joint. Rarely do the conventional roentgenograms depict changes in the cartilaginous coverings and the interposed fibrocartilaginous discs and plates; the main value is in ruling out other pathologic conditions. In our series, normal roentgenograms were obtained for 72 per cent of the patients.

SUMMARY

In making the diagnosis of internal derangement of the knee joint, a history of injury, the presence of an effusion and tenderness are more significant than either the presence of a click or the history of locking. However, not one of these is diagnostic in every instance.

It is rare for a patient to have an internal derangement of the knee joint without a history of injury. Sometimes the alleged injury may be entirely coincidental or may be the effect rather than the cause of the pathologic condition.

An evaluation of the clinical findings as correlated with the pathologic findings is made for fifty-seven patients who had an arthrotomy of the knee joint. Six patients were found to have apparently normal surfaces of the joint at surgery and three had synovitis, giving a minimum of 15 per cent who did not benefit from their operative procedure. The relative constancy of the standard abnormal findings is mentioned.

PRACTICAL SURGICAL SUGGESTION

Improved Simple Manual Dermatone

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A SIMPLE manual dermatone adapting the mechanical principles of the hand-operative hair clipper was reported in 1958.* (Fig. 1.)

After further trial it was decided that the instrument would be more useful in the hands of a larger number of surgeons if the safety razor blade used as a cutting element oscillated more rapidly and if the thickness of the graft could be altered. Accordingly, the Durham-Duplex safety razor blade was mounted in a stainless steel and aluminum housing with a roller placed so as to determine the thickness of the graft. (Fig. 2.) Rollers of different size were made so that they could be substituted to vary the thickness from twelve-thousandths to twenty-thousandths of an inch.

* BATE, J. T. A simple manual dermatone. *Am. J. Surg.*, 97: 90, 1959.

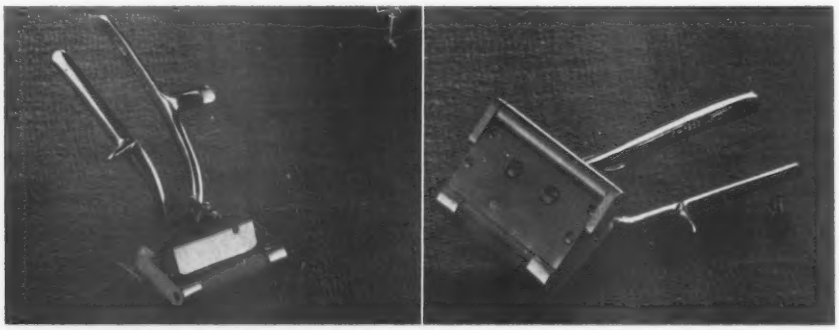

FIG. 1A and B. The previously reported manual dermatone (skin-clipper, fourth model). A, anterior surface view. B, under surface view.

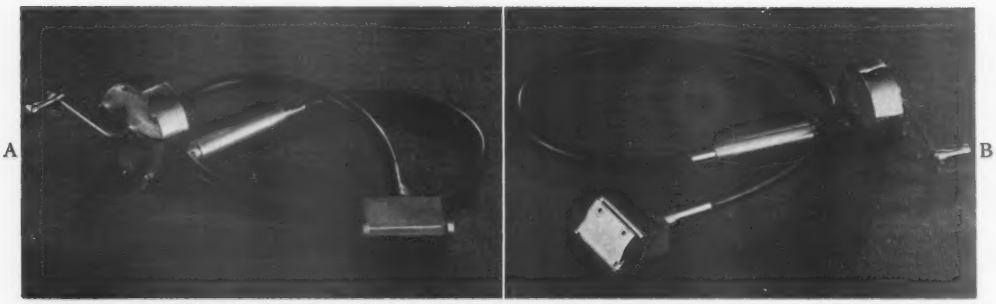

FIG. 2. Improved manual dermatone. A, anterior surface view. B, showing under surface with safety razor blade in place.

A short cable connected the driving element to a set of gears enclosed in an anodized aluminum housing and motivated by a hand crank. The entire instrument can be autoclaved.

Either side of the blade can be used for cutting the graft. It is easily inserted by removing a plate held in place by two set screws. An Allen wrench is used for this purpose.

TECHNIC

After preparing the donor site, which is usually the thigh, the instrument is placed so that the cutting edge of the safety razor blade and the roller are in contact with the skin. The anterior part of the instrument is held between the thumb and index finger of one hand and the posterior part between the thumb and index finger of the other hand. It is not necessary to apply saline solution or a lubricant to the skin. The crank is turned rapidly by an assistant or by any sterile or unsterile personnel. The surgeon slowly advances the instrument until the graft begins to show above the roller. It can be allowed to accumulate here or an assistant can lift it out with two mosquito forceps so that the length can be seen. Grafts 2 to 4 inches long and $1\frac{15}{16}$ inches wide have been cut by this method. The thickness can be varied by changing the roller from twelve-thousandths to fifteen-thousandths, eighteen-thousandths or twenty-thousandths of an inch.

The last model of this instrument was fitted with a handle. This is used to guide the instrument rather than having to hold it with the index finger and thumb of each hand.

Acknowledgment: The improved instrument has been made possible by the suggestions and cooperation of Mr. Marshal Morrison, Director of Research, The Orthopedic Frame Company, Kalamazoo, Michigan.

A New Diagnostic Sigmoidoscope for General Use

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IN 1956 we became interested in more reliable lighting in sigmoidoscopes. We had frequently been disturbed by lamps burning out at a critical stage of the procedure, causing annoying delays and often resulting in the added expense and inconvenience of bringing the patient back to the operating room at a later time.

It was our further belief that the highly desirable wider use of sigmoidoscopy as a method of detection of cancer by general practitioners, internists and surgeons, as well as proctologists and gastroenterologists, was being somewhat inhibited by lack of a suitable instrument. The development of a sturdy, reliable, inexpensive sigmoidoscope, we thought, would promote more frequent inclusion of sigmoidoscopy as part of routine physical examinations.

We found that a manufacturer of these instruments was already working intensively along these same lines and joined efforts with him in the development of such an instrument.* It was intended principally for diagnostic use, as in our opinion other already existing instruments would be more suitable for operative procedures.

Sigmoidoscopy is an aid in early detection of polyps. Swinton [1] found 15 to 20 per cent of polyps undergo malignant changes. Between 70 to 80 per cent of cancers of the large bowel are detectable through the sigmoidoscope. Cattell [2] has found that malignant change may occur in ulcerative colitis.

Too much dependence is placed on barium enema. It must be kept in mind that a blind area is present in the rectum and rectosigmoid during barium enema. A good principle would be always to precede barium study of the colon by sigmoidoscopy.

In this connection, digital and anoscopic examinations are also important for complete study. The best approach consists of digital and anoscopic examination and sigmoidoscopy followed by a barium study.

Lamphier [3] states that "sigmoidoscopy should precede every barium enema examination. In order to avoid the chance of error, there should be no exception to this rule." In like fashion, no hemorrhoidectomy should be performed without being preceded by sigmoidoscopy.

These two principles require a large number of sigmoidoscopies. Yet, even physicians who agree with these principles do not always follow them because sigmoidoscopy frequently is a nightmare of technical difficulty with the light bulb burning out and connections coming apart at crucial points of the procedure.

The ideal instrument would employ a larger, sturdier lamp which would be less apt to burn out. The instrument would be so constructed that if the lamp did burn out, it could be replaced quickly during examination without the necessity of removing and reinserting the sigmoidoscope. It would require a minimum of special equipment not ordinarily found in a general practitioner's office.

The production instrument, as now available,

*The sigmoidoscope described herein is manufactured by Welch Allyn, Inc., Skaneateles Falls, New York.

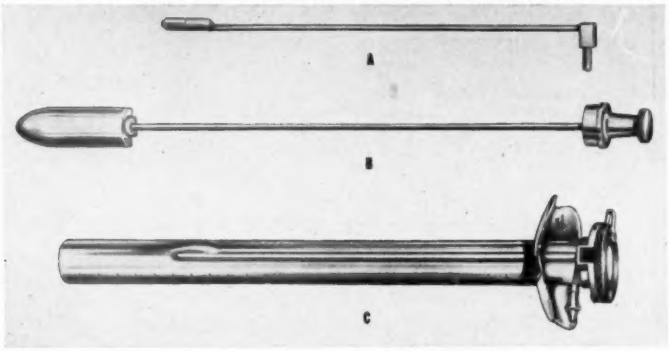

FIG. 1. New diagnostic sigmoidoscope.

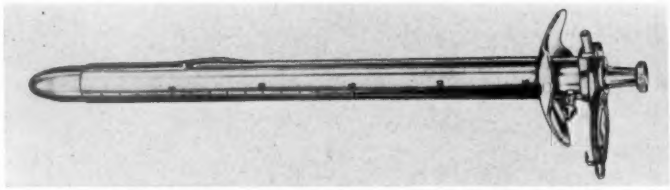

FIG. 2. New diagnostic sigmoidoscope, assembled.

meets these requirements to an extraordinary degree. It uses the same brilliant and long-lived lamp customarily used in otoscopes. For a light source, it employs the same battery handle used almost universally for otoscopes and ophthalmoscopes, with ordinary flashlight batteries which may be obtained anywhere or the newer rechargeable batteries.

Such battery handles have their own rheostat, and intensity of illumination can be adjusted by a flick of the thumb. Even when used at maximal intensity for long periods, the voltage from these battery handles will not burn out the lamp, yet illumination is more than adequate. A further advantage is that no separate battery boxes or transformers need to be purchased.

Large sized lamps such as this have not previously been used for distally illuminated sigmoidoscopes because their presence at the distal end of the speculum seriously impeded both visibility and instrumentation. This objection has been overcome by having the lamp recessed in a "blister" in the wall of the speculum, large enough to remove it from the visual field but not so large as to present any problem in insertion of the sigmoidoscope.

The lamp screws into the end of a long light carrier (Fig. 1A) and is connected by a cord to the battery handle. Cord connections, both to the light carrier and the battery handle, are positive and cannot accidentally be disconnected during examination. The light carrier is slipped into the tube provided for it in the wall of the speculum before the sigmoidoscope is inserted, yet it can easily be removed for cleaning or on the rare occasions when lamp replacement is necessary, without removing the sigmoidoscope.

The obturator (Fig. 1B) is inserted after the light carrier is put in place and removed after the sigmoidoscope is introduced. There is a small but adequate amount of illumination at the end of the scope even when the obturator is in place, which allows insertion of the sigmoidoscope without requiring extra light.

Figure 1C shows the speculum. The lens is rotated into place after the obturator is removed giving a closed system. The inflating bulb attaches to the proximal end of the speculum to aid in distention of the bowel during introduction of the sigmoidoscope.

This channel for inflation goes out to the distal portion of the speculum. It can be used also as a built-in smoke removal tube during cauterization.

The complete instrument, with light carrier and obturator in place, is shown in Figure 2. It is a sturdy, reliable and relatively simple sigmoidoscope which should make the recommended wide use of sigmoidoscopic examination more practical.

SUMMARY

This new model sigmoidoscope is sturdy and reliable for heavy-duty diagnostic use. It makes sigmoidoscopy an easier, quicker procedure and should further the wider use of sigmoidoscopy as part of routine physical examinations, thus aiding in early detection of cancer.

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Depth Perception in Proctoscopy

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AREAS of doubt and inaccuracy of interpretation are still present in proctoscopy. One which contributes to the lessened accuracy derives from the flat vision with no stereopsis caused by the narrow confines of the tube. This is the necessary result of monocular vision. Doubtlessly, extensive experience helps to compensate in some measure for this difficulty. However, in the average situation no sense of depth is present. Therefore, distances are undetected and rounded eminences and irregularities are more difficult to recognize. When a snare or forceps is introduced, there is a corresponding amount of inaccuracy and what might be termed poor marksmanship when attempting to achieve accurate placement for biopsy or polyp removal. In contrast, binocular vision through a tube gives depth perception and reduces these difficulties.

Presented herein is an instrument adapted and resurrected from one once used in Vienna for depth perception in laryngeal examinations.* Lighting has been removed. The critical focal length has been increased, oculars have been made adjustable and, in general, there has been considerable simplification. The basic reflecting and transmitting visual system is also similar to that found in two indirect ophthalmoscopes now in common use.

The optical system is similar in many ways to that found in field binoculars or stereoscopic operating microscopes. There is a lens in front of each eye. Directly ahead of this is a vertical mirror set at a 45° angle to the line of gaze. In the center between the two mirrors is a prism with the apex forward. (Figs. 1 and 2.)

FIG. 1. Illustration of use of depth perceptor through proctoscope.

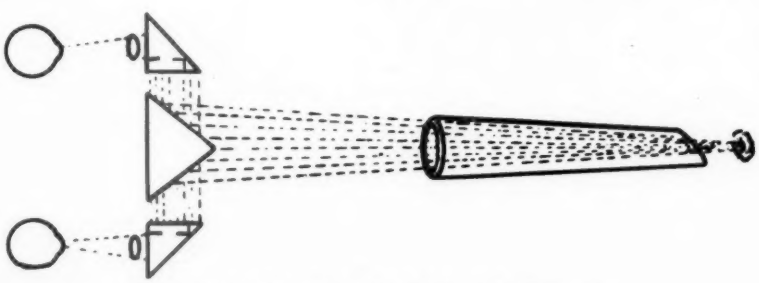

FIG. 2. Illustration of optical principle of depth perceptor.

*Manufactured by V. Mueller and Company, Chicago, Illinois.

The line of vision, therefore, moves forward from each eye to the mirror. It is then reflected at a right angle to fall on the outer surface of the prism. Thus, the two rays are projected forward down the proctoscope tube.

In optical effect both eyes are used but the interpupillary distance is reduced to less than the diameter of the examining tube. The lenses can possess magnification. They are adjustable and can be held in a fixed position. During adjustment the plane mirrors slide with the viewing lenses permitting variation to compensate for the varied interpupillary distance of different operators. Since two eyes are used there is depth perception and stereoscopic vision. This is easily demonstrable with a tube through which pins are placed at varying distances when first viewed with one eye and then through the instrument.

Similar visual problems exist in direct laryngoscopy which are solved by using the same type of instrument.

CASE REPORTS

Extraperitoneal Thoracic Aorta to Femoral Bypass Graft as Replacement for an Infected Aortic Bifurcation Prosthesis

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INFECTIONS developing in plastic arterial prostheses, although fortunately rare, have grave consequences when they occur and usually result in the loss of lives or extremities depending upon the location of the arterial replacements. The plastic arterial substitute acts as a foreign body, so that once bacteria invade its fibers, the infection becomes resistant to all known modes of therapy and will resolve only if the prosthesis is removed.

The case herein reported emphasizes the lethal nature of infection around arterial substitutes. It describes a method of bypassing the intraperitoneal infection following removal of an infected aortic bifurcation graft to avoid ischemia of the pelvis and lower extremities.

CASE REPORT

C. T., a sixty-six year old white man, underwent resection of a symptomatic abdominal aortic aneurysm at the San Francisco Veterans Administration Hospital on June 26, 1960. The aorta was replaced with a woven Teflon® bifurcation graft extending from 1 inch below the renal arteries to the common iliac vessels just above their bifurcations. The immediate postoperative course was uneventful except for a low grade fever which developed in the second postoperative week and which responded to the administration of antibiotics for ten days. He was discharged on July 17 and did well for the subsequent three weeks.

He was readmitted on August 7, six hours after the sudden onset of severe abdominal pain, with a pulsatile mass in the mid-abdomen. Emergency laparotomy disclosed a large retroperitoneal hematoma. Proximal and distal control of the aorta was obtained and a 1 cm. rent was noted in the proximal anastomosis. In addition to the fresh clot, induration of the retroperitoneal tissues extended into the mesosigmoid and the base of the mesentery. After removal of the graft and resection of the friable aortic stump, the occluding aortic clamp was placed temporarily above the renal arteries and a knitted Teflon bifurcation graft was sutured to the cuff thus provided just below the renal vessels. The friable common iliac arteries were oversewn and the legs of the graft anastomosed end to side to the external iliac arteries. Cultures of the retroperitoneal tissues taken at surgery revealed a heavy growth of Escherichia coli. It was assumed that infection caused the disruption of the graft. The postoperative course was marked by a persistent fever of 102 to 103°F. that gradually subsided on large doses of chloramphenicol, streptomycin and penicillin.

On September 6, four and a half weeks after placement of this last graft, he was again rushed to the operating room with severe abdominal pain and shock. Again, there was disruption of the proximal anastomosis, and gross sepsis was present. After proximal and distal control was obtained with the proximal clamp again placed above the renal arteries, the graft was removed and the stump of the aorta oversewn with heavy chromic catgut sutures. The external iliac arteriotomies were closed with fine running sutures. The retroperitoneum was left open and the abdomen closed with retention sutures.

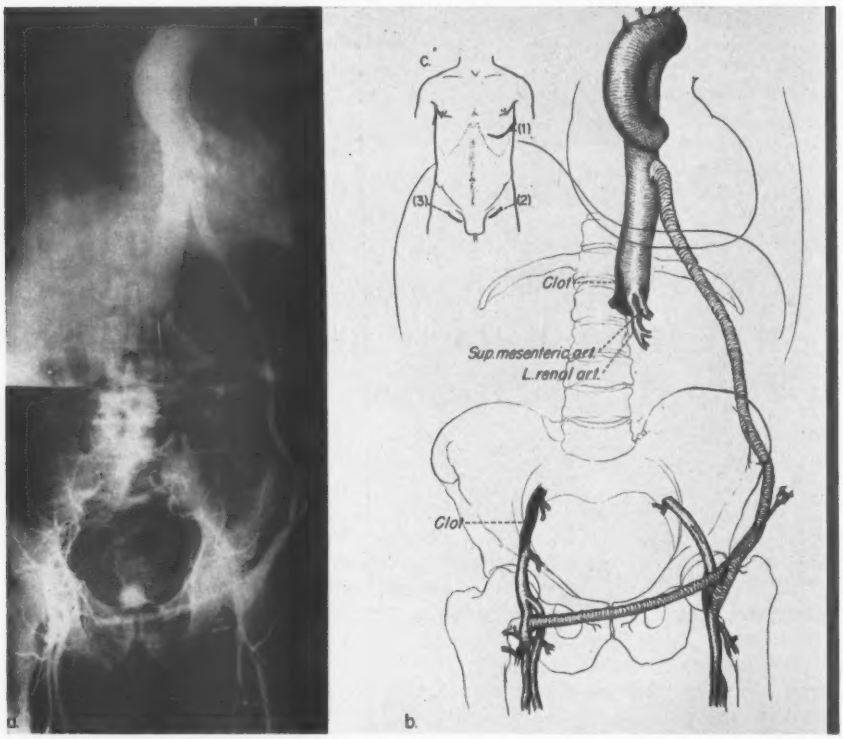

FIG. 1. Thoracic aorta to femoral bypass. A, roentgenogram of injected graft at time of postmortem examination. B, diagram showing location of bypass graft depicted in A. C, diagram of location of incisions for placement of graft: (1) thoracic incision, eighth interspace, (2) left femoral incision, (3) right femoral incision.

Because of severe ischemia of the lower trunk and legs evident at the completion of the operation, the patient was re-prepped and draped. Incisions were made in the left groin to expose the femoral artery and in the left side of the chest, using an anterolateral approach through the eighth interspace, to expose the descending throacic aorta. (Fig. 1C.) A partially occluding clamp of the Satinsky type was placed on the lower descending thoracic aorta and a knitted Dacron® graft measuring 14 mm. in diameter was anastomosed end to side to the aorta. A retropleural plane of dissection was developed posteriorly toward the pleural sulcus, then carried through the sulcus out under the twelfth rib to a plane just beneath the lumbodorsal external oblique fascia. A tunnel was then dissected bluntly using a Yankauer suction tube inserted obliquely, posteriorly and laterally around the iliac crest and this was connected to the femoral incision by tunneling under the sartorius muscle. The graft was then passed through the tunnel and sutured to the side of the left femoral artery. The right femoral artery was exposed, a knitted Dacron tube measuring 10 mm. was sewn to the 14 mm. tube just above the left femoral anastomosis, and this smaller graft was passed through a subcutaneous tunnel across the pubis and sutured to the right femoral artery. At the completion of the operation (Fig. 1B) the lower portion of the body was warm and pedal pulses were palpable in both lower extremities.

The immediate postoperative course was relatively benign. Massive doses of antibiotics were given to combat the coliform organisms which again were cultured from the retroperitoneal tissue at the time of surgery. The patient was gradually mobilized and the pulses in the feet remained good on sitting and on ambulating. There was a low grade fever which persisted from the time of surgery. In the third postoperative week a spiking fever developed with evidence of toxicity and the course from that time on was gradually downhill. He died on October 9, four and a half weeks after the last operation, and despite terminal shock, the graft remained patent to the time of death. (Fig. 1A.)

Autopsy revealed a large retroperitoneal abscess with numerous intraperitoneal loculations of pus.

The right kidney was atrophic and the origin of the right renal artery was occluded by clot which occupied the oversewn end of the aortic stump. The grafts were patent throughout their course and were free of infection.

COMMENTS AND CONCLUSIONS

This case report emphasizes the disaster associated with infections in plastic arterial replacements. The patient was fortunate enough to survive two ruptures of a proximal aortic graft anastomosis and died of infection in the retroperitoneum despite removal of the foreign material and a successful bypass of the infected area with an extraperitoneal aorta to femoral bypass. The retroperitoneum was not drained because of proximity of the bypass to the left flank. In retrospect, it would have been advisable to drain the left retroperitoneal area at the last operation and run the bypass down on the right side. The graft was inserted with some trepidation even though it was believed that the infected area had been scrupulously avoided, because of the possibility of metastatic infection of the circumventing graft from septicemia. This did not prove to be a problem in the present case as the graft and surrounding tissues remained free of infection while the patient eventually died four and a half weeks later of overwhelming intra-abdominal sepsis.

It is believed that the bypass graft from the thoracic aorta to the femoral arteries via an extraperitoneal tunnel is a satisfactory way of maintaining the distal circulation. This might again be employed in similar circumstances in which infection in or around the abdominal aorta precludes the local use of a prosthesis. When infection develops around a graft that bypasses occlusive disease, it would seem preferable to simply remove the graft and rely upon previously existing collaterals to maintain the viability of the distal tissues. If no arterial obstruction existed prior to placement of a graft, as in this case of resection of the aneurysm, ischemia is usually more profound and often not compatible with survival. In this instance, a bypass procedure of the type described herein may permit salvage of an otherwise desperate situation.

SUMMARY

This article re-emphasizes the grave consequences of infection about prosthetic arterial grafts and offers a potential solution to this problem when it involves an abdominal aortic prosthesis. A pertinent case report describes the removal of such an infected aortic prosthesis and the successful use of a graft system, leading from the distal thoracic aorta to both femoral arteries, bypassing the infected abdomen entirely.

Spontaneous Perinephric Hematoma Secondary to Renal Tumor

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SPONTANEOUS perinephric hematomas are usually caused by bleeding from a kidney or, less commonly, from adjacent structures in the retroperitoneal space. The underlying cause of the bleeding may be due to a wide variety of disease processes which have been documented in the literature by many observers [*1–14*]. The hematoma may be confined by the true capsule of the kidney (subcapsular) or lie between the true capsule and Gerota's fascia (extracapsular). In rare cases, it may extend beyond Gerota's fascia into the retroperitoneal space downward in the retrocolic gutter. Actual rupture through the peritoneum with bleeding into the peritoneal cavity has also been reported [*14*]. This presentation comprises two case reports of spontaneous perinephric hematoma secondary to a renal tumor.

CASE REPORTS

CASE 1. An acute spontaneous perinephric hematoma was found between the renal capsule and Gerota's fascia (extracapsular) which was secondary to rupture of a large carcinoma of the kidney.

This patient, a forty-seven year old Negro man (O. P.), was admitted to the Cook County Hospital on May 6, 1959 with a three day history of intermittent severe pain in the right flank and right upper quadrant associated with nausea and vomiting. There were no bowel or urinary symptoms. There was no previous history of abdominal or flank pain.

Physical examination revealed a well developed man who appeared in good condition. The conjunctivas were pale. The abdomen was moderately distended with marked tenderness and moderate rigidity in the right costovertebral angle and right upper quadrant. No masses were palpable. The remainder of the results of physical examination were negative. The patient's blood pressure was 112/42 mm. Hg, his temperature was 102°F. and his pulse was 112 per minute.

Laboratory studies revealed the hematocrit was 17 per cent and the hemoglobin was 9.8 gm. per cent. The urinalysis and the blood urea nitrogen, creatinine and electrolytes were normal. A roentgenogram taken of the abdomen with the patient in a flat position showed no unusual bowel pattern or soft tissue mass. The outline of the kidneys could not be defined. There was no free air or fluid level.

The patient was given supportive treatment consisting of blood transfusions, intravenous fluids, antibiotics and gastric suction. His general condition rapidly improved with subsiding of the pain and tenderness on the right side. The blood pressure remained stable, the pulse rate became normal and the hematocrit rose to 28 per cent. An intravenous pyelogram taken two days after admission showed a normal left upper urinary tract with incomplete visualization of the right kidney. A right retrograde pyelogram revealed the right kidney deviated downward and laterally. The lower calyces were normal but the middle calyces and pelvis were pushed downward and the upper calyces were not visible. The impression was a mass involving the upper pole of the kidney.

Exploration of the right kidney was performed on the fifth hospital day through a subcostal incision in the flank. On opening Gerota's fascia, a large hematoma was encountered compressing the entire kidney. The blood was evacuated and a large mass was seen at the upper pole of the kidney. While attempting to free the kidney, severe bleeding occurred from the upper pole mass. This could only be controlled by applying two clamps to the region of the renal pedicle as quickly as possible and removing the kidney. Ligature of the renal pedicle could not be satisfactorily accomplished so the clamps were left in place together with a small gauze pack. During the procedure, 4 pints of blood were administered. The patient was taken from the operating room; his blood pressure was

FIG. 1. Case I, removed kidney, unopened with surrounding extracapsular hematoma covering almost the entire kidney. The lower pole is visible and free of clots. At the upper pole is a tumor mass surrounded by the hematoma.

90/60 mm. Hg and his pulse rate was 120 per minute.

The postoperative course was without complications with no evidence of bleeding. Three pints of blood were given during the immediate postoperative period and the hematocrit rose to 40 per cent on the third postoperative day. The clamps and packing were removed on the seventh postoperative day. The patient was discharged on June 15, 1959 with the wound healed.

The pathologic report included the following data: The specimen consisted of a kidney weighing about 300 gm., measuring 10.2 by 8.5 by 6.5 cm. The renal parenchyma proper appeared normal but at the upper pole adjacent to the pelvic lining there was a round soft mass 5.5 cm. in diameter which was well circumscribed and consisted of bright yellow to dull pink material with much superimposed hemorrhage and large clots. Blood clots coated a large portion of the renal surface. The renal pelvic lining was smooth. The renal artery was traced and found to be of uniform caliber. The renal vein was patent and empty. (Figs. 1 and 2.)

Microscopic sections taken through the round mass revealed extensively necrotic and hemorrhagic tissue with homogeneously pink staining, fairly uniform-appearing clusters composed of more or less rounded pale cells with small nuclei in the background. (Fig. 3A and B.) The diagnosis was adenocarcinoma of the kidney.

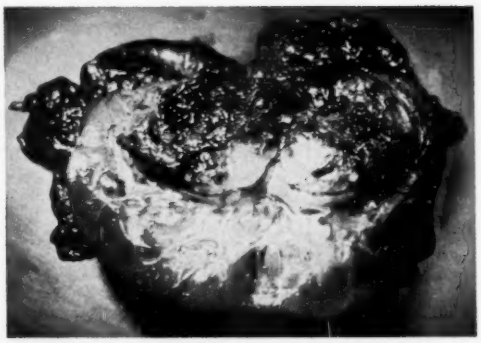


FIG. 2. Case I, removed kidney, sectioned, to show the tumor mass at the upper pole with adherent blood clots.

CASE II. This is a case of an acute spontaneous perinephric hematoma, confined by the renal capsule (subcapsular), secondary to rupture of a small carcinoma of the kidney.

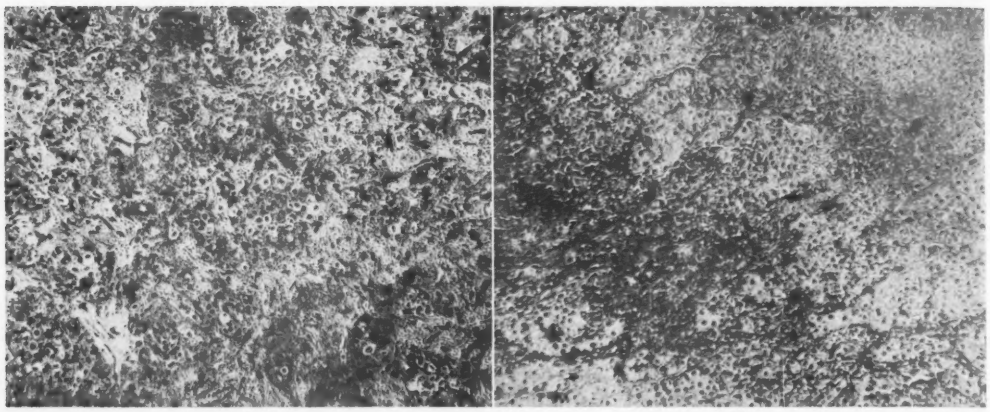
A fifty-six year old white man (A. G.) was admitted to the Michael Reese Hospital on May 23, 1960 with a one day history of acute severe pain in the right flank and right upper quadrant associated with nausea and vomiting. There were several loose bowel movements but no changes in the color of the stool. There were no urinary symptoms.

Physical examination revealed a well developed man in moderate distress. The pertinent findings were confined to the abdomen with marked tenderness and moderate rigidity in the right costovertebral angle and right upper quadrant. No masses were palpable. The patient's blood pressure was 130/90 mm. Hg, his temperature was 100.4°F. and his pulse rate was 98 per minute.

Laboratory studies revealed a normal blood count with a hemoglobin of 13.1 gm. per cent and a hematocrit of 40 per cent. The results of urinalysis were negative except for 3 to 5 million red blood cells per cu. mm. and 7 to 8 million white blood cells per cu. mm. The results of chemical analysis of the blood including a liver profile were entirely normal. A roentgenogram of the abdomen with the patient in a flat position was normal. The clinical impression was acute cholecystitis.

The patient improved rapidly and was afebrile in forty-eight hours. The abdominal pain and tenderness subsided and the patient became asymptomatic. He was discharged on May 28, 1960; arrangements were made to have further x-ray studies performed on him as an outpatient.

Following discharge, he was readmitted because of chills and fever with a temperature to 101.6°F. and mild discomfort in the right flank. There was moderate tenderness in the right flank and right upper quadrant but no mass was palpable. A repeat blood count revealed a hemoglobin of 10.9



A B

FIG. 3. A and B, (Case 1) microscopic sections of renal tumor showing clusters of carcinoma cells with adjacent necrotic and hemorrhagic tissue.

FIG. 4. Case II, intravenous pyelogram showing a large mass involving the right kidney with pressure on the pelvis and calyces.

FIG. 5. Case II, retrograde pyelogram confirming the presence of a right renal mass and medial deviation of the upper right ureter.

gm. per cent and a hematocrit of 34 per cent. A low grade fever persisted. On the fourth day, a tender mass was palpable in the right upper quadrant and right flank.

X-ray studies indicated the gallbladder and the large bowel were normal. An intravenous pyelogram showed a normal left upper urinary tract. There was a large mass on the right side obliterating the outlines of the right kidney, displacing the right ureter medially and pressing upon the calyces which were otherwise well defined. (Fig. 4.) A retrograde pyelogram on the following day revealed essentially the same findings. (Fig. 5.) The clinical impression was that of a renal tumor.

FIG. 6. Case 11, removed kidney with perinephric hematoma. Capsule around hematoma has been opened showing partially organized blood clots. Intact kidney is not visible.

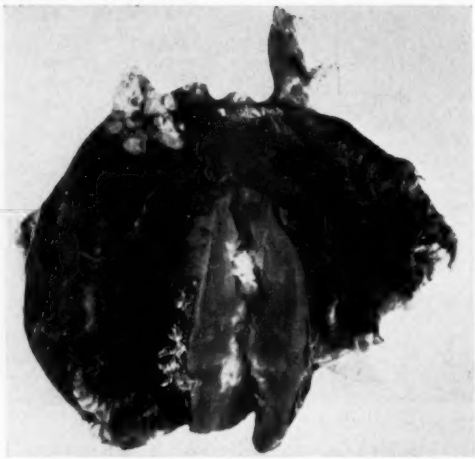


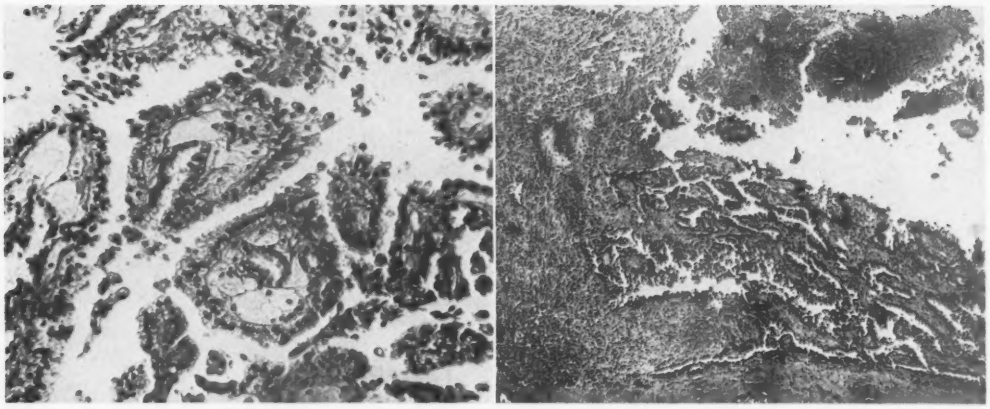
FIG. 7. Case 11, removed specimen, sectioned to show normal appearing kidney surrounded by adherent subcapsular hematoma.

On June 9, 1960, exploration of the right kidney was performed through an incision in the eleventh intercostal space in the flank. On opening Gerota's fascia and separating the perinephric fat, a large soft bluish mass was seen attached to and compressing the underlying kidney. The kidney, together with the attached mass, was separated from the surrounding tissue and a nephrectomy was performed.

The postoperative course was without complications except for a low grade fever which persisted for one week. There was moderate purulent drainage from the wound which subsided by the time of discharge on June 25, 1960.

The pathologic report included the following: The specimen consisted of a kidney surrounded by perinephric fat which together measured 15 by 8 by 5 cm. The external surface of the perinephric fat showed large hemorrhagic areas over the convex border of the kidney, and over the hilum. In these areas, the fat tissue was hemorrhagic throughout the entire thickness. Between the capsule and the kidney there was a large hemorrhage which had been previously opened and evacuated. (Figs. 6 and 7.) The hemorrhage covered approximately one third of the convex kidney surface. The capsule stripped with ease over the rest of the cortex. The kidney itself measured 10.5 by 6 by 4 cm. in diameter and weighed 130 gm. The cortical surface was pinkish red and granular over both poles. The cortex measured approximately 0.5 cm. in thickness, and showed no gross abnormalities. The medulla was grey-pink and normal in appearance. The mucosa of the pelvis and the calyces showed a few petechial hemorrhages. On the cortical surface close to the hilus, there was a yellowish white soft nodule measuring 0.6 cm. in diameter. Sections from the nodule were labeled *A*. At the hilus there was a segment of ureter which measured approximately 2.5 cm. in length and 0.3 cm. in diameter. Its mucosa was pink-white and glistening. There were also several stumps of arteries and a vein which measured from 0.5 to 1 cm. in diameter. In one area, the convex surface of the cortex was depressed and covered by gray-red friable material and blood; the superficial portion of the cortex in this area was firm and showed grey discoloration.

Microscopic examination revealed the following: Sections of the kidney labeled *A* showed extensive hemorrhage beneath the capsule, and in one area a tumor apparently had arisen from the surface of the kidney. The tumor was extensively fragmented on the surface away from the kidney and mingled with masses of red blood cells so that only a narrow rim of the tissue of the tumor remained attached to the surface of the kidney. Fragments of similar papillary tumor were present in sections of the hematoma from the kidney capsule. The tumor consisted of numerous papillary and some glandular structures lined by cuboidal and columnar epithelial cells with eosinophilic cytoplasm and round or oval basophilic nuclei. There was some variation in the shape and the staining qualities of the cells; some were rather large and pale. There was focal capsular invasion. In several sections there were several well circumscribed papillary tumors within the



A B

FIG. 8. Case 11. A, microscopic section (high power) of renal tumor demonstrating papillary mixed adenocarcinoma. B, Microscopic section (low power) of surface of renal tumor showing papillary adenocarcinoma with adjacent necrotic tissue and organizing hematoma.

cortex of the kidney which were not well demarcated from the surrounding tissue. The cells covering the papillary stalks were small and cuboidal. (Fig. 8A and B.) The diagnosis was papillary mixed adenocarcinoma of the kidney of low grade malignancy with massive subcapsular hemorrhage, multiple papillomas (hamartomas) of the kidney and pyelitis cystica.

COMMENTS

The first authoritative description of perinephric hematoma is attributed to Wunderlich in 1856 [*11*] and for many years was referred to as Wunderlich's disease. Since that time, and especially in the past thirty years, numerous case reports and several reviews of the literature have been published. Polkey and Vynalek [*1*] found 178 cases in the literature to 1929. Uson [*11*] found references to 300 case reports in the years preceding 1959. Since there are undoubtedly many more cases which have not been reported, it would seem that spontaneous perinephric hematoma is not as rare as is commonly thought and could be diagnosed preoperatively more often if physicians were aware of this condition.

A comprehensive study of the causes of spontaneous perinephric hematoma was made by Polkey and Vynalek [*1*]. Of 178 cases reviewed, the location was subcapsular in 18.5 per cent and extracapsular in 81.5 per cent. Diseases of the kidneys and its blood vessels accounted for 92 per cent of the cases. The more common etiologic conditions were nephritis (thirty cases), tumors (twenty-two cases), renal artery aneurysm (twenty cases), arteriosclerosis (twelve cases), hydronephrosis (seven cases), periarteritis nodosa (seven cases) and tuberculosis (four cases).

There were eleven cases (6 per cent) secondary to diseases of the adrenals. Blood dyscrasias occurred in 4.5 per cent. Of interest was that no renal disease could be found in twenty-six cases (14.6 per cent). This is difficult to explain on any physiologic basis but must be accepted in view of the many authenticated reports in which a careful pathologic examination of the kidney was performed by a competent pathologist.

In recent years a surprisingly large number of cases due to periarteritis nodosa have been reported. Rolnick [*3*] has suggested that many of the earlier cases diagnosed as nephritis may have been actually periarteritis nodosa which were misdiagnosed because of incomplete knowledge of this disease. Since the clinical picture of periarteritis nodosa is being recognized much more frequently, this assumption appears to have validity.

Inasmuch as nephrectomy is often performed for perinephric hematoma, it is important to consider whether the underlying cause is due to unilateral renal disease or to a systemic condition involving both kidneys. In the presence of a renal tumor, hydronephrosis, renal artery aneurysm, lithiasis or unilateral renal tuber-

culosis, nephrectomy does not present any significant long term problem. On the other hand, if the etiology is nephritis, arteriosclerosis, periarteritis nodosa or a blood dyscrasia and nephrectomy must be performed as a life-saving procedure, careful follow-up observation of the remaining kidney must be maintained.

The relatively high incidence of renal tumors as an etiologic factor is worthy of note. The symptoms due to the perinephric hematoma may be the first clinical manifestation of a renal tumor as occurred in the two patients reported on herein. In the first patient, the tumor was large so that the probability of a cure is unlikely. In the second patient, however, the tumor was small and, fortunately for the patient, the hemorrhage necessitated nephrectomy which was performed early enough to warrant a hopeful outlook. If a perinephric hematoma does develop in the early stages of the tumor, before spread has occurred, the possibility of a cure by nephrectomy is, of course, much more likely.

The presenting clinical picture of perinephric tumor is unrelated to the basic underlying pathology. In essence, the picture depends upon the rate of bleeding which falls into two general groups: the acute form and the subacute or chronic form.

With acute bleeding, the clinical picture consists of a sudden onset of severe pain in the flank or abdomen, tenderness and rigidity on the involved side and evidence of internal bleeding. Pain, tenderness and rigidity may be due to many diverse conditions involving the kidney or intra-abdominal organs and may be associated with nausea, vomiting and abdominal distention. If there are concomitant signs of internal bleeding, the presence of a perinephric hematoma should be suspected. With severe bleeding, the patient may be in shock with tachycardia, hypotension, pallor and profuse perspiration. With lesser degrees of bleeding, these signs may be absent, but a drop in the hemoglobin or hematocrit is a common finding. This is an extremely important diagnostic feature of perinephric hematoma and should arouse suspicion of the possibility of this lesion. If there is any question, daily determinations of the hemoglobin and hematocrit should be carried out which will establish the presence of internal bleeding.

The pain and tenderness are usually localized to the flank but may also involve the upper or lower abdominal quadrants depending upon the location and size of the hematoma. If the hematoma extends downward in the retrocecal region, the picture resembles acute appendicitis with the result that a laparotomy is performed. This has been reported by several observers [*4,6,13*]. Localization of the pain and tenderness in the right upper quadrant due to an anterior position of the hematoma may simulate acute cholecystitis. Rarely, perforation into the peritoneal cavity may occur causing a generalized peritonitis. However, in general the presenting clinical picture is that of a renal colic with pain and tenderness localized in the region of the flank.

In the acute form, a mass is usually difficult to palpate immediately because of the marked rigidity of the muscles and extreme tenderness. After the pain has subsided and the patient is more comfortable, a palpable mass may be apparent unless the hematoma lies posteriorly to the kidney. However, with a large hematoma which has extended anteriorly or inferiorly a mass can usually be felt. If the hematoma is subcapsular, it may not become particularly large because of the confining affect of the renal capsule. However, this layer is somewhat elastic and the subcapsular hematoma in our second patient was at least the size of the kidney. Although the perinephric space is limited by Gerota's fascia, this is not a fixed structure and the perinephric areolar and fatty tissue is potentially distensible to a large degree. A hematoma within this space can develop to an enormous size before sufficient pressure occurs to cause tamponade of the bleeding site. In the event that the hematoma breaks through Gerota's capsule downward into the retrocolic gutter, the mass can extend as far down as the inguinal region and displace the colon immediately.

With subacute or chronic bleeding, the pain is not severe and has usually been present for a longer time. For these patients the principal findings are a low hemoglobin and a palpable mass.

The preoperative diagnosis of perinephric hematoma is rarely made because this condition is not common and, more important, is rarely considered by the examiner. An intravenous or retrograde pyelogram may demonstrate an enlarged kidney or other evidence of renal disease but is not pathognomonic. A retro-

peritoneal mass adjacent to the kidney may be seen but its exact nature cannot be ascertained. There may be varying degrees of pyelectasis and calycectasis if there is obstruction of the ureter or pelvis. Displacement of the kidney or deviation of the upper ureter because of the retroperitoneal mass is often present depending upon the size and location of the hematoma. On the basis of pyelographic studies, the diagnosis is usually either renal tumor, perinephric tumor or perinephric abscess. A perinephric hematoma should be suspected if in addition to these findings there has been a drop in the hemoglobin or hematocrit.

There has been almost unanimous opinion in the literature that nephrectomy should be performed as soon as possible. The statistical studies on mortality rates seem to confirm this view. Of the 178 cases analyzed by Polkey and Vynelack, sixty-two patients had nephrectomy with a mortality of 24 per cent. Conservative surgery consisting of incision, drainage and packing in forty-three cases resulted in a mortality of forty per cent. There was a 100 per cent mortality in forty-seven cases in which supportive measures were used and surgery was not performed. It is obvious that nephrectomy may be a life-saving measure in the presence of persistent bleeding and is definitely indicated with unilateral renal disease as the underlying cause. However, in a significant number of patients the removed kidney failed to reveal any pathologic lesion, or the underlying disease was bilateral. If the hematoma is not large and if adequate visualization of the site of bleeding from the kidney can be obtained so that it can be controlled with sutures, a biopsy of the involved renal tissue may be preferable to nephrectomy. It is apparent that these conditions will be met infrequently but in the event they do occur, a needless or hazardous nephrectomy may be prevented.

Another precaution that should be observed is the assurance that there is a normally functioning kidney on the opposite side; whenever possible this should be verified by a preoperative intravenous pyelogram. If laparotomy is performed as a result of a mistaken diagnosis of an acute surgical abdomen and a retroperitoneal mass is seen, it may be advisable to either close the abdomen or drain the hematoma through a retroperitoneal stab wound. The status of the opposite kidney can be determined afterwards with an intravenous pyelogram, and a secondary renal exploration through the flank can be performed following recovery from the laparotomy.

SUMMARY

1. Two case reports of spontaneous perinephric hematoma secondary to renal tumor are presented. In the first patient, the hematoma was extracapsular and the tumor was large. The second patient had a subcapsular hematoma and the kidney appeared grossly normal. Microscopic examination revealed a small carcinoma in the cortex which was the cause of the bleeding.

2. The etiology of spontaneous perinephric hematoma includes a multiplicity of disease processes, the more common being nephritis, renal tumors, renal artery aneurysm, arteriosclerosis and periarteritis nodosa. It is of interest that no renal disease could be demonstrated in a significant number of reported cases.

3. The possibility of a renal tumor being the cause of the bleeding should be kept in mind since a spontaneous hematoma may be the first clinical sign of this lesion.

4. The diagnosis of perinephric hematoma is rarely made since the clinical picture and pyelographic findings are not pathognomonic. It should be suspected in all patients with a history of pain in the flank and presence of a renal mass together with evidence of internal bleeding. The most important diagnostic feature is low or decreasing hemoglobin and hematocrit.

5. The treatment of choice is nephrectomy which is often a life-saving procedure. However, whenever possible the status of the opposite kidney should be determined preoperatively since the underlying cause of the bleeding may be bilateral.

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Innominate Artery Loop as a Pulsating Mass in the Neck

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ANEURYSMS near the bifurcation of the innominate artery or in the common carotid artery are quite rare. DeBakey and Crawford [1] have reported one with successful removal and replacement by a homograft. Pulsatile masses occurring behind the right clavicle or in the lower right side of the neck are more common, however, and it is important to determine their exact nature.

Although this mass may be an aneurysm, a substernal thyroid or a parathyroid cyst, it usually will be a tortuous kinked innominate or common carotid artery. The first anatomic mention of this was by Coulson [2] in 1852, as an autopsy finding. Brown and Rowntree [3] in 1925 reported several such clinical cases of pulsating masses due to this tortuous vessel.

FIG. 1. Angio-aortogram showing elevated aortic arch and complete loop of innominate artery.

In 1952 Deterling [4] presented a comprehensive review of the subject, and Stone and Lord [5] have recently reported on it.

If the tortuous vessel occurs in the neck a definite diagnosis can be made by careful physical examination. Occasionally the pulsatile mass is in a lower position behind the clavicle. In this instance an angio-aortogram or a dye study made by direct needle puncture of the pulsating mass will establish the diagnosis.

The exact diagnosis is important. If the mass is an aneurysm, excision is indicated. If the mass is a loop of innominate or carotid artery, however, no direct surgical therapy is advisable. Instead, attention is directed to the associated hypertension.

CASE REPORT

Mrs. N. S., a seventy year old white woman, presented with a pulsating mass just behind the right clavicle. It had been present for two years and had increased gradually in size. Except for high blood pressure her health had been good.

Examination revealed a blood pressure of 200/130 mm. Hg in both arms. The pulsating mass, which measured 4 by 6 cm. in size, was just behind the right clavicle. A systolic bruit was present.

Routine laboratory work and serology tests were within normal limits. A chest roentgenogram showed an elevated aortic arch but no mediastinal mass.

An angio-aortogram using 90 per cent Hypaque® solution demonstrated clearly that the mass actually was a complete coil of the innominate artery just proximal to its bifurcation. (Fig. 1.) There was no aneurysm.

The patient was reassured and given appropriate treatment for the hypertension. No surgery was performed.

COMMENTS

Since surgical excision of aneurysms has become feasible, there has been considerable

interest in various pulsating masses. Although a pulsating mass behind the right clavicle may be an aneurysm, it is far more likely to be a loop of innominate or carotid artery. The exact diagnosis can be made easily before any operative exploration is considered.

Although such a loop may appear on the left side, it usually occurs on the right side and is most commonly seen in elderly hypertensive women. The pathogenesis is apparently an atherosclerotic elongation of the vessel associated with an elevated aortic arch. Local symptoms are rare and ordinarily the loop should not be removed. Instead, management is directed toward the associated hypertension.

SUMMARY

A case of an innominate artery loop occurring low in the right side of the neck is presented. The exact diagnosis was established by angioaortogram. The occurrence of these loops is discussed and the importance of distinguishing them from aneurysms is emphasized.

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Gastrocolic Fistula Secondary to Carcinoma of the Stomach

MANAGEMENT OF AN UNUSUAL CASE SURVIVING SIX YEARS AFTER RADICAL OPERATION

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CARCINOMA of the stomach as a primary cause of gastrocolic fistula appears to be decreasing. This must be due to the fact that patients seek earlier treatment as a result of accurate diagnostic roentgenographic studies which are performed more frequently. There are some indications that this malignancy is actually decreasing in frequency as well. Hence, large growths are not permitted to develop. Nevertheless, from time to time, a patient seeks treatment for a large complicated lesion which at first, seems hopeless.

Gastrocolic fistula, secondary to carcinoma of the stomach, is such a lesion. Patients with this disease represent a challenge to the surgeon from several directions. The disturbed physiology in these patients leads to profound disturbances in fluid balance, to anemia and dangerous malnutrition. Infection in the area of the fistula is an added hazard. Yet these tumors have occasionally shown peculiar behavior whereby the growth, although large, remains relatively well localized. Distant metastases occur late. Patients with these tumors are excellent candidates for radical operations which may achieve gratifying palliation from a malignancy which not long ago would have been considered inoperable. Since limited ablative and bypass procedures are still being performed, this matter needs discussion. We believe that insufficient time and effort are expended in the preoperative preparation of these seriously ill patients. They should not be rushed to the operating room in a state of emergency. After a period of treatment, even the most desperately ill patients will be able to withstand a formidable procedure.

The following case report illustrates such a problem and presents the management in detail.

CASE REPORT

The patient was a fifty-seven year old white man, first seen on February 22, 1954, in the emergency room, having lost 60 pounds (from 175 to 115) in one year. The four chief symptoms were fecal vomiting, weight loss, gaseous eructation and an abdominal mass. Specifically, diarrhea was not a prominent symptom. The patient took milk of magnesia every evening to insure daily bowel movements. The stools were described as light in color and the urine dark. He had vomited twice daily during the previous three days, and the vomitus had the color, odor and gross characteristics of feces. There was no coffee-ground material in the vomitus, no hematemesis and no melena. His appetite had remained fair, except for the previous two days, when he had lost the desire for food. He had not had jaundice. He had not felt well for the preceding fourteen months, and during the past eight months had noted a slightly tender mass in the left upper quadrant. A striking feature was that the patient had not sought medical help for a period of eight months after he noted a mass in his abdomen, as it caused him little discomfort.

On physical examination, the patient was well developed but poorly nourished and appeared chronically ill. Weight loss was apparent, as his skin covered the musculoskeletal prominences loosely. Pallor was obvious. Blood pressure was 94/60 mm. Hg, pulse 76 per minute, and temperature 99°F. Examination of the tongue showed a glossitis. Abdominal examination revealed a mass measuring 8 by 10 cm. in the left upper quadrant of the abdomen. This was relatively nontender and

could be palpated easily. Rectal examination revealed no mass or rectal shelf.

Clinical impression included carcinoma of the stomach, carcinoma of the colon or possibly gastrocolic fistula. The patient was admitted to the hospital from the emergency room.

Laboratory findings on admission were as follows: hemoglobin was 10.6 gm. per cent; red blood cell count 3,870,000 per cu. mm. and white blood cell count 14,200 per cu. mm. Serum albumin was 2.9 gm. per cent and globulin 2.1 gm. per cent. Urinalysis showed a specific gravity of 1.02, and the urine was negative for sugar and albumin. Nonprotein nitrogen was 36 mg. per cent and the CO_2 19.2 mEq./L. Serology was negative. Blood chemistry was otherwise normal.

When the patient was given a soapsuds enema in preparation for studies for a barium enema, he promptly vomited the soapsuds. This pertinent observation prompted the diagnosis of gastrocolic fistula to be made before the barium enema roentgenogram was available. The validity of this observation was confirmed by barium enema examination when the gastrocolic fistula was clearly demonstrated. Barium enema examination, or oral barium, give the best objective evidence of the correct diagnosis. The size of the lesion in our patient and the fistula are seen in Figure 1. A diagrammatic representation of the lesion is shown in Figure 2.

Early treatment was designed to restore hydration of the patient and to correct his anemia and hypoproteinemia. After admission a right transverse colostomy was performed to interrupt the fecal stream from reaching the fistula between the stomach and colon. (Fig. 3.) This was accomplished with the patient under local anesthesia because of his poor condition. The severe malnutrition was corrected by the insertion of a small-lumened feeding tube, which was passed through the stomach and duodenum into the jejunum beyond the fistulous opening. This detail, we believe, is of inestimable value since it permitted alimentation of the patient, whereby food and electrolytic requirements could be met without resorting to intravenous therapy. An operative jejunostomy was avoided. Liquefied whole food was then given through the small tube and increased daily; eventually 2,000 cc. of liquefied whole food and multiple vitamins was given through this small tube. Paregoric was given to decrease excessive activity of the bowel, since this was at times stimulated by the administration of the whole liquefied food.

While these details were carried out, careful preparation was being made for radical surgery. Neomycin was instilled into the distal colostomy stoma for two days prior to the radical surgery. He was given aerosol inhalations of penicillin for his chronic bronchitis. Antibiotics were given daily, as were multiple vitamins. His intake and output of fluids was carefully observed to maintain a proper state of hydration. Definitive operation was not undertaken until March 13, 1954 (twenty-one days after admission), when it was believed that the patient represented a reasonable risk.

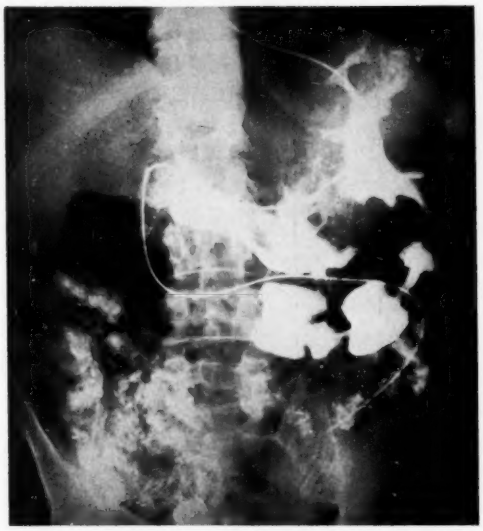


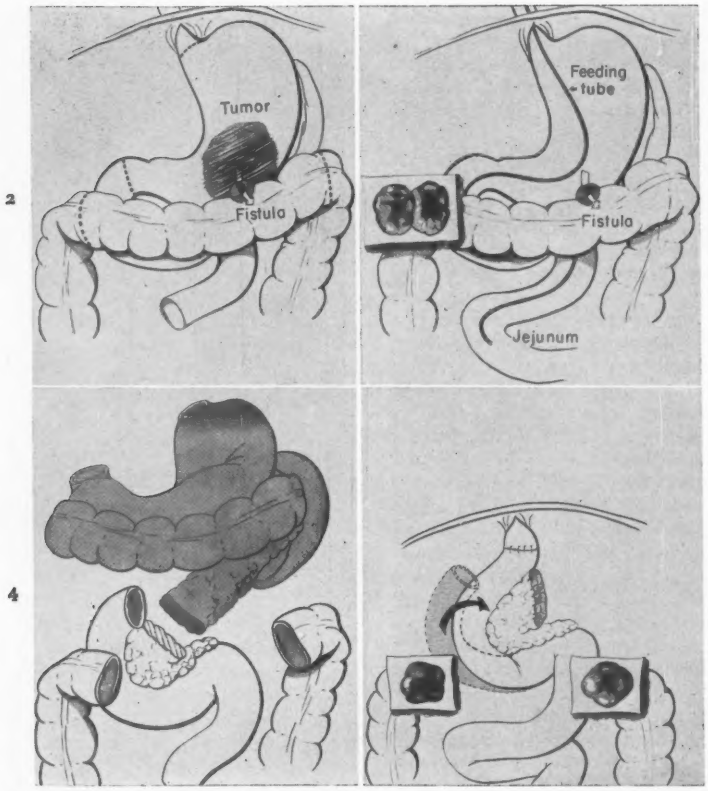
FIG. 1. Roentgenogram of the stomach showing large filling defect and fistulous communication between stomach and colon.

Surgery consisted of the following: total gastrectomy, omentectomy, splenectomy, transverse colectomy and partial pancreatectomy. (Fig. 4.) Intestinal continuity was restored by performing an esophagoduodenostomy. (Fig. 5.) The principle employed here is not new, of course, but its application in this particular case is of interest because the tumor and the surrounding area of possible metastases were excised *en bloc*.

The patient's postoperative course was complicated by a small fistula originating at the anastomotic site, but which closed in less than five weeks. After recovery from this procedure, the colostomy was closed on June 15, 1954, and the patient was discharged from the hospital seventeen days later.

The pathologist's report was as follows: upon opening the stomach a large, fungating ulcer was seen. (Fig. 6A.) This was 10 cm. in diameter and located on the greater curvature. In the center of the ulcer was an opening which penetrated the stomach wall and entered the transverse colon. (Fig. 6B.) The spleen, a portion of the pancreas and the omentum were also examined.

Microscopic sections through the stomach and colon showed masses of atypical glands which



2 3 4 5

FIG. 2. Drawing showing the fistula between the stomach and colon, and the area to be excised *en bloc*.

FIG. 3. Preliminary right transverse colostomy shown in drawing. A very important detail shown here is that the feeding tube is passed through the stomach, beyond the fistula and into the jejunum.

FIG. 4. Drawing showing tissues excised *en bloc* in shaded area. Omentum has been omitted so as not to obscure important details.

FIG. 5. Drawing showing esophagoduodenostomy and colostomy. Duodenum has been mobilized anteromedially as described by Kocher. The colostomy was subsequently closed.

extended completely through the stomach wall. (Fig. 7.) A heavy infiltration of chronic inflammatory cells was present. The tumor did not extend to the mucosa of the colon in these sections. Lymph nodes and sections of the spleen and pancreas showed no tumor. The diagnosis was adenocarcinoma of the stomach.

The patient was seen from time to time and gained weight. On June 3, 1955, he weighed 134 pounds and was doing light work as a maintenance man for a rooming house. He stated that he was taking six small feedings per day and continued to be active. On June 4, 1959, he was seen for the specific purpose of evaluating his hemopoietic system. He was getting along well and working daily. His tongue looked normal. Specifically, there was no lymphadenopathy and abdominal examination failed to reveal any masses. The blood smears showed evidence of splenectomy, but no evidence of pernicious anemia. Hemoglobin was 14.1 gm. per cent. The conclusion was that the patient did not have the entire stomach removed, or else he has some functioning gastric rests in the esophagus or duodenum.

The patient was last seen on February 20, 1960, with herpes zoster, and again careful studies were carried out. Postoperative barium swallow revealed no malignancy. (Fig. 8.) Despite extensive studies,

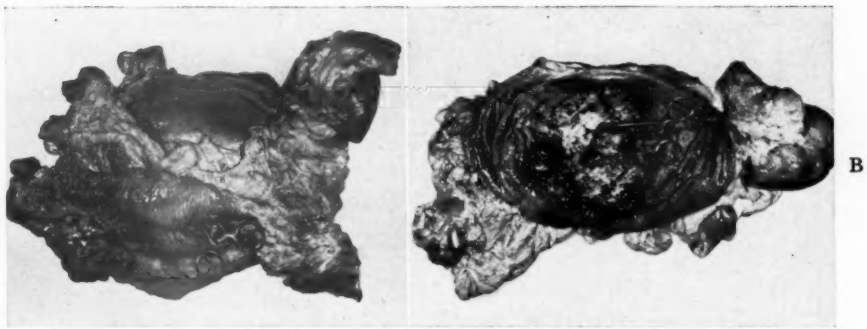


FIG. 6. A, photograph of actual specimen and fistula seen from colonic side. B, photograph of actual specimen and fistula seen from gastric side. Note large fungating, ulcerating lesion.

no malignancy was found. Thus, the patient with this radical operation has been followed up for six years, with no clinical evidence of recurrence.

COMMENTS

Fistula formation between the stomach and colon may be due to peptic disease and its complications, but we are concerned herein with gastrocolic fistulas arising secondarily to carcinoma of the stomach or colon. These patients are seriously ill and depleted as a result of the malignancy and, in addition, suffer severe nutritional disturbances. Infection is present as well in the inflammatory and neoplastic adherent mass between the stomach and colon. Starkey-Smith [*23*] described a case simulating enteric fever. The nutritional deficiencies are manifest clinically by weight loss, emaciation, dehydration, edema, ascites, pallor, glossitis, neuritis, ecchymoses, tetany and night blindness.

From the standpoint of the clinical laboratory, hypoproteinemia, anemia, depressed blood ascorbic acid values and prolonged Quick prothrombin time have been recorded by Atwater et al. [*2*]. Megalocytic anemia simulating sprue was observed by Fairley [*10*].

Before discussing a plan for management of these patients, we would like to recall the causes of death that have been observed most often

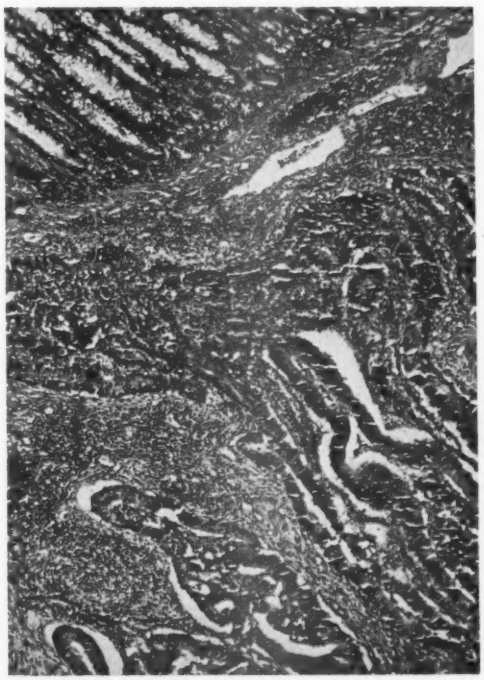


FIG. 7. Photomicrograph of the lesion showing normal colonic mucosa above and neoplasm below.

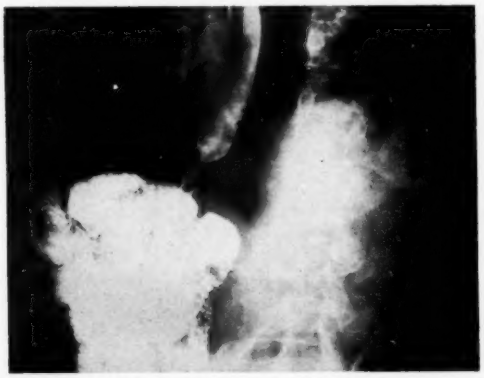


FIG. 8. Roentgenogram of esophagoduodenal anastomosis six years postoperative.

in the past. We agree with Marshall [17] who lists (1) peritonitis, (2) shock, (3) pulmonary complications: pneumonia and embolism, (4) hemorrhage, (5) cardiac failure and (6) renal failure, as the most common causes of death in these patients. At least four of these dangers can be modified today by careful preoperative preparation.

There are several advocates for the single stage operation (i.e., resection of the fistula and adjacent organs and restoring intestinal continuity), including Gray [10], Localio [15], Keshishian [14] and Marshall [18]. These authors were dealing with gastrojejunocolic fistulas.

Staged operations, in which a preliminary colostomy was performed, were recommended by Pfeiffer [21], Barber [4], Mathewson [19] and Lowden [16]. Baker [3] favored an ileostomy as the short-circuiting procedure. These were similarly employed in gastrojejunocolic fistulas. Colp [9] described an unusual case in which a fistula of the transverse colon healed after preliminary colostomy in the ascending colon.

We recognize the advantages of a single stage operation and are certain that there are many occasions for its use. Yet in selected patients some benefit must be claimed for performing a preliminary colostomy. We first saw our patient in the emergency room, acutely ill, dehydrated and malnourished. We divided his care into these phases:

I. Emergency treatment:
   - A. Correct dehydration with intravenous fluids.
   - B. Replace needed electrolytes.
   - C. Correct anemia and hypovolemia.
   - D. Combat infection with broad spectrum antibiotics.
   - E. Perform colostomy of the right transverse colon.

II. Intermediate care requiring several days:
   - A. Improve nutrition by providing protein, fat, carbohydrates, vitamins and minerals.
   - B. Combat infection.

III. Definitive treatment:
   - A. Excise the fistula and adjacent organs involved with tumor.
   - B. Reconstruct the gastrointestinal tract either at this time as (a), or later.

We would like to emphasize that after the patient's dehydration is corrected and his blood volume restored, a right transverse colostomy is performed with the patient under local anesthesia. Naturally, this is utilized in the seriously ill patient.

Feeding is carried out by inserting a polyethylene tube into the upper jejunum and beyond the gastrocolic fistula. (Figs. 1 and 3.) According to Pareira [20], tube feeding (intragastric) was practised by John Hunter in 1776, who described one of his mixtures as follows: "It should be used to inject jellies, eggs beat up with a little water, sugar, milk or wine, by way of food, and that the medicines might be mixed with it." Since that time there were many physicians who realized the value of some type of tube feeding. Jones [13] in 1916, Abbott [1] in 1940, and Bockus [6] in 1944 have described variants in the technic of tube feeding.

A great variety of foods may be used in restoring the patient's nutrition. We have favored liquefied whole food and its administration through a fine No. 240 polyethylene tube under pressure of a pump, as suggested by Barron [5]. We were unable to get sufficient volumes of the liquefied food into the jejunum by gravity flow alone, hence the use of a mechanical pump. Utilizing this technic, it is possible to provide adequate caloric intake and the following daily dietary requirements for a 70 kg. active man, as reported by Jeans [12]: protein, 70 gm.; calcium, 1 gm.; iron, 12 mg.; vitamin A, 5,000 international units; thiamine, 1.5 mg.; riboflavin, 1.8 mg.; niacin, 15 mg.; ascrobic acid, 75 mg.; folic acid, 1 to 2 mg.; and vitamin K, adequate in any good diet.

After three weeks of preparation, which included the use of antibiotics, the patient's condition was such that he tolerated a radical total gastrectomy, splenectomy, partial pancreatectomy and transverse colectomy. The colostomy was closed at a subsequent operation.

At the present time, over six years after his surgery, the patient is alive and well. Brunschwig [7] was a pioneer in the employment of radical surgery for extensive malignancies. He emphasized the palliative and curative value of aggressive surgical treatment of tumors, even when the lesion is quite large.

Marshall [18] reported on six patients with carcinoma of the colon and complicating gastrocolic fistula surviving longer than thirteen months following radical surgery for such lesions. One of his patients survived sixty months. Ransom [22] described a patient in whom he performed an *en bloc* resection of the

colon and stomach. The result was a survival of over two years. Clay and Ravitch [8] reported survivals of thirty and forty-two months. They point out that not infrequently, when faced with resectable lesions, the surgeon may choose to perform limited resection or even a bypass procedure, thus depriving the patient of the excellent palliation that comes with removal of a large tumor.

We would like to encourage the careful evaluation of every patient with malignancy, to give each the palliation and relief of symptoms that come with removal of large tumors. Bypass procedures offer these patients little real relief. Limited resections may disseminate the tumor. Generalized peritoneal implants and multiple hepatic and distant metastases are the important limiting factors when dealing with such malignancies. Other tumors that can be mobilized, even though large, should be removed with a reasonable amount of adjacent tissues. No patient should be abandoned as "inoperable" until resectability has been carefully weighed in every case.

In the postoperative period intensive care is extremely important as well. Ambulation must be practiced early and throughout the convalescence. Deep breathing exercises and avoidance of atelectasis are important. Intravenous fluids are necessary until peristalsis returns. After that liquefied food is used to provide adequate proteins, vitamins and minerals.

CONCLUSIONS

A case of gastrocolic fistula secondary to carcinoma of the stomach is presented.

Careful preparation was carried out preoperatively with intravenous fluids and blood transfusions.

Interruption of the fecal stream by performing a colostomy proximal to the fistula is an important preliminary step.

Intrajejunal administration of whole liquefied food via a small-lumened tube permits restoration of nutrition after the colostomy is functioning. The importance of this phase of treatment cannot be overemphasized.

En bloc excision of the stomach, omentum, transverse colon, spleen and two thirds of the pancreas was then accomplished.

Long term palliation is possible, even in dealing with large complicated lesions in the absence of distant metastases.

Our patient survived six years after the extensive procedure and is still alive and active.

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The Air-Sucker's Gastric Rupture Syndrome

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THE purpose of this report is to call attention to a rare and catastrophic complication of surgery which has occurred during or shortly after operations on the mouth or throat. There is reason to believe that it could appear during almost any operative procedure. A case is presented herein of gastric rupture in a child complicating a routine tonsillectomy and adenoidectomy. No similar case has been observed at this hospital. Comments concerning the classic clinical features, the etiology, the pathogenesis and the treatment of the air-sucker's gastric rupture syndrome are included.*

CASE REPORT

A nine year old white boy was admitted to the hospital for elective tonsillectomy and adenoidectomy. Surgery was recommended because of recurrent upper respiratory infection, subnormal hearing, adenoid facies and breathing through the mouth. The patient's history was without medical incident except for the usual childhood diseases and rickets, all of which had responded to the appropriate therapy leaving no sequelae. The family history was not contributory.

Physical examination revealed a thin boy whose size was normal for his age. The vital signs, heart, lungs, abdomen, genitalia and extremities were normal. The tonsils were moderately enlarged without injection or exudate. Breathing through the mouth was apparent. The eyes, ears and nose were normal. The hemogram and the results of urinalysis were normal.

On October 14, 1958, the patient was taken to the operating room. At 10:10 A.M. anesthesia was induced with drop Vinethene® and followed by open drop ether over a mask. During the dissection, ether was insufflated through an oral Gwathmey ether hook. The patient was not intubated and positive pressure was not used. No swallowing motions were noted.

At 10:20 A.M., by means of sharp and blunt dissection, the otorhinolaryngologist mobilized and amputated the tonsils with a snare. A chromic catgut suture was placed in the left tonsillar fossa to control bleeding. The adenoids were removed with an adenotome and bleeding from this area was controlled with a pack. For the final minutes of the procedure the patient was noted to be cyanotic. His color improved after administration of the anesthetic was terminated.

At 11:00 A.M. the patient was taken to the recovery room. Shortly after his arrival, it was noticed by the nurse that the patient was cyanotic with tachycardia and rapid shallow respirations. He had not reacted from the anesthetic. Further examination demonstrated a massive distention of the abdomen with tympany on percussion. Acute gastric dilatation was suspected and a Levin tube immediately inserted. Only a small amount of gas and bloody fluid could be aspirated.

At noon the abdominal x-ray films demonstrated a massive "tension" pneumoperitoneum with marked bilateral elevation of the diaphragm. (Fig. 1.) At 12:15 P.M. an abdominal paracentesis was quickly performed to relieve the severe intra-abdominal tension. As the 13 gauge needle entered the peritoneal cavity, gas whistled noisily through the needle sounding like a tire going flat. The gas smelled strongly of ether. As the patient's abdomen decompressed, his respiratory exchange and color quickly improved and he was soon responding to verbal stimuli.

The patient was then prepared for exploration and definitive control of what was suspected as gastrointestinal perforation. The preoperative diagnosis was probable rupture of the stomach secondary to gastric dilatation. Ruptured esophagus from retching and perforated duodenal ulcer were considered as alternate diagnostic possibilities.

The patient was anesthetized at 1:05 P.M. for an exploratory celiotomy; the peritoneal cavity was entered through a left upper paramedian incision.

* We considered a more dignified name such as aerophagic's gastric rupture syndrome but discarded it as unscientific. Aerophagia, to most, means the swallowing of air. The mechanism in this syndrome is not the swallowing of air, rather it is the sucking of air.

A B

FIG. 1. A and B, these x-ray films were taken immediately after tonsillectomy and show the massive "tension" pneumoperitoneum due to gastric rupture.

The abdominal viscera were all normal except the stomach which was torn. A 1.5 cm. rent involving the anterior wall of the pars media near the lesser curvature was identified. (Fig. 2.) The mucosa was prolapsed through the rent. Extending distally from this full thickness opening was a serosal tear 3 cm. in length. It appeared to be a simple rupture due to bursting as no ulceration, granulation or induration was present. The gastric rent was closed in two layers. The abdominal wall was closed in layers. The patient's condition was stable throughout the operative procedure.

The patient was treated postoperatively with gastric suction, intravenous fluids and chloramphenicol. He was ambulant on the first postoperative day and was taking oral fluids on the second. By the fourth day he was afebrile and eating well. He experienced more pharyngeal pain from the tonsillectomy than abdominal discomfort. He was discharged to go home on the seventh postoperative day. He has been asymptomatic for the last twelve months.

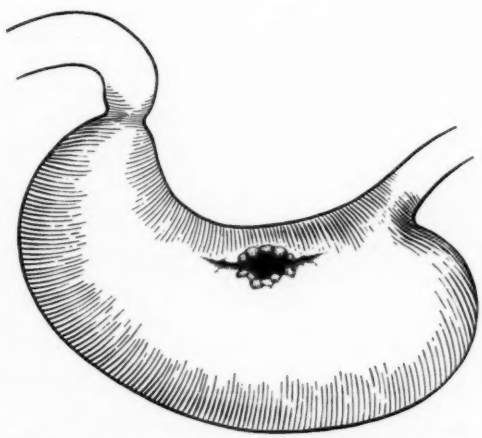

FIG. 2. Depicted above is the "burstlike" tear of tissue of the lesser curvature of the stomach. The diameter of the tear was 1.5 cm.

ETIOLOGY AND PATHOGENESIS

Figure 1 demonstrates clearly that the peritoneal cavity contained much more than one "stomach-full" of gas. We believe that the large amount of offensive gas was *air ingested rapidly from the atmosphere of the room* before and following the gastric perforation. It does not seem possible that several liters of gas could be produced in a few minutes by fermentation within the stomach or by diffusion from the blood stream. Furthermore, much evidence has been gathered that ingested air is the main source of gastrointestinal gas whenever it is present [1,2].

The fundamental questions to be answered are (1) how was all the air ingested and (2) what prevents this from happening during the usual case? The key to answering these questions is a structure called the superior *esophageal sphincter* or the cricopharyngeal sphincter [9]. The work of Maddock and his co-workers [2–4] has been especially helpful in elucidating the mechanisms involved in the intake of external air into the gastrointestinal tract. According to their studies, this superior esophageal sphincter is normally tonically closed and acts as a watchdog, preventing the entrance of inspired air into the esophagus. When a person eats, the swallowing reflex opens the sphincter to allow food to enter the esophagus. Some patients are able to swallow or gulp air without food (aerophagia), usually as an involuntary neurotic habit, producing various aerophagic syndromes [1]. There is, however another mechanism for ingesting external air into the gastrointestinal tract. If the superior esophageal sphincter is relaxed and the glottis closed, *air may be sucked into the esophagus by inspiration*. Inspiration produces negative intraesophageal and intragastric pressures as well as negative intrathoracic pressure. Patients with esophageal speech, persons who guzzle beverages and those who belch have developed voluntary control over this sphincter, which contains striated muscle. They suck, not swallow, the air or beverage past the relaxed sphincter by inspiratory effort. Maddock and associates [3,4] believe that many so-called "aerophagics" do not actually swallow air but are, in reality, involuntary suckers of air. Surgical procedures, anesthesia and pain may relax this important sphincter thereby causing acute gastric dilatation [4].

The patient reported herein is a voluntary sucker of air. His mother reported that he teases his siblings by belching loudly at them on frequent occasions. He was also an involuntary sucker of air during the tonsillectomy. His reactive *superior esophageal sphincter apparently relaxed during tonsillectomy in response to anesthesia or operative manipulation. This allowed the ingress of atmospheric air causing massive gastric dilation with gastric rupture.* No swallowing was noted during or after anesthesia.

A second etiologic factor in this patient may have been obstruction of his airway. During the final minutes of the tonsillectomy, the patient was noted to be cyanotic; his color improved after anesthesia was terminated. The most likely cause of the cyanosis, obstruction of the airway, could promote sucking of air in two ways. First, respiratory obstruction produces increased respiratory effort. With deeper inspiration there occurs greater negative intraesophageal and intragastric pressures [4] to aspirate air into the esophagus. Secondly, if the larynx were obstructed by a sagging epiglottis, the air that would normally enter the glottis would be shunted into the gastrointestinal tract. Maddock, Bell and Tremaine [2] commented that distention has developed in some of their patients whose airways were obstructed; they measured intake of 780 cc. of air in one patient with intermittent airway obstruction.

A third etiologic factor was considered, studied and dismissed. It is known that liquid ether, when it vaporizes, expands to over 400 times its normal volume [10]. Because aspiration with a needle of our patient's pneumoperitoneum produced air with a strong odor of ether, we at first considered it possible that liquid ether might accidentally have entered the hypopharynx. However, investigation revealed that the mask was covered with several layers of gauze at all times. Experiments by the Anesthesia Department further demonstrated that drop ether could not be poured rapidly enough, under the conditions of administration of the anesthetic to this patient, to allow liquid ether to pass through the gauze into the pharynx.

The data in three similar cases found in the literature [3,5,6] and in our case are summarized in Table 1. The authors in one case were unable to determine whether the air entered via the gastrointestinal or the genital tract and they stated, "the mechanism leading to the pneu-

TABLE 1
DATA ON REPORTED CASES OF GASTRIC RUPTURE SYNDROME

Author and Year	Age (yr.)	Sex	Operation	Anesthetic	Treatment	Postoperative Course
Maddock et al. (1949) [3]	47	F	Dental root extraction	Intravenous sodium pentothal	Exploration and closure	Without complications
Rogers and Jones, 1951 [5]	15	F	Tonsillectomy and adenoidectomy	Open drop ether	Gastric suction for two weeks, then exploration	Small bowel obstruction requiring surgery
McGreane, 1959 [6]	8	M	Tonsillectomy and adenoidectomy	Drop ether, drop Vinethene, ether insufflation	Gastric suction	Without complications
Olsen and Foley, 1959	9	M	Tonsillectomy and adenoidectomy	Drop ether, drop Vinethene, ether insufflation	Exploration and closure	Without complications

moperitoneum is obscure" [5]. The author of another unexplored case suggested that air entered through the gastrointestinal tract but he had no evidence that such was the case [6]. Our finding of a ruptured stomach during exploration made it clear that the gastrointestinal tract was, indeed, the portal for the air. Identical findings were obtained for the other patient who was subjected to early exploratory celiotomy.

TREATMENT

Should these patients be treated with gastric intubation and suction or should they be subjected to surgical exploration? Both methods of therapy have been used. (Table 1.) The only reason offered to support the nonoperative treatment has been that "it is probable that a minute break in the wall of the gastrointestinal tract occurs, allowing gas—but not solid or liquid—to enter the peritoneal cavity" [6]. Although there is considerable evidence to suggest that pneumoperitoneum following gastroscopy may be due to a minute break in the gastric wall [7], that is manifestly not the case in patients with this gastric rupture syndrome. Our patient at exploration had a sizeable tear of the gastric wall measuring 1.5 cm., while the rent in the stomach of the patient reported by Maddock measured 4.5 cm. [3]. Many cases of perforated peptic ulcer have been treated successfully by gastric suction [8], but again the perforations from ulcers are much smaller than those in the patients with the type of gastric rupture with which we are concerned herein.

We believe that these patients with gastric rupture *should be treated surgically*, not just medically. This approach seems prudent not only because those patients observed at surgery have had sizeable rents, but also because it is simply impossible to predict preoperatively how far the gastric tear has extended. One patient who was not treated surgically had the complication of obstruction of the small bowel; he ultimately required surgery [5].

After the diagnosis of air-sucker's gastric rupture syndrome has been made, preferably with roentgenographic confirmation, the pneumoperitoneum should be decompressed by paracentesis with a needle. This definitely improves the general status of the patient by increasing respiratory and circulatory efficiency. The dyspnea and cyanosis disappear and the pulse rate returns to reasonable levels. An exploratory celiotomy should be performed as soon as the patient's condition becomes stable. There is no value in giving Prostigmine® or stimulants to the central nervous system. Postoperative antibiotics should not be necessary as the stomach is empty when rupture occurs.

CONCLUSIONS

1. Gastric rupture with massive pneumoperitoneum is a rare complication of operations on the mouth or throat. Usually, the operative procedure is tonsillectomy.

2. The tonic contraction of the superior esophageal sphincter (cricopharyngeal sphincter) normally prevents the intake of such large quantities of air into the gastrointestinal tract.

3. If this sphincter is relaxed in response to anesthesia or reflexes from dissection, large quantities of air may be sucked into the stomach by inspiratory effort. Acute gastric dilatation followed by gastric rupture may occur.

4. Proper treatment consists of decompression of the pneumoperitoneum by paracentesis with a needle followed by an operative procedure to close the tear in the gastric wall.

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Kultschitzky-Cell Carcinoma (Carcinoid) of the Appendix with Metastasis

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THERE have been approximately 1,000 cases of "carcinoid" of the appendix reported in the literature including some thirty cases of appendiceal carcinoids with metastases [*1,3,4,7–9,12*].

The first authentic case of carcinoid of the appendix was reported by Beger in 1882 [*2*], but Hand et al. [*6*] state that Ransom in 1880 reported a case of carcinoid with metastasis.

These tumors were first thought to be carcinomas but because of their apparent benign nature, the term "carcinoid" was coined in 1907 by Oberndorfer [*10*] and has become the most widely accepted term used to refer to these tumors.

When it became evident that many of them showed some evidence of invasion of the muscularis and serosa of the appendix, the term adenocarcinoma grade 1 was suggested [*13*]. With further study, the tumor cells were found to be argentaffin positive and the terms argentaffinoma and argentaffin carcinoma were introduced.

Eldred [*4*] suggested the term Kultschitzky-cell carcinoma as most appropriate since these tumors are known to arise from the normally occurring specialized granular cells of Kultschitzky in the base of the crypts of Lieberkuhn. This explains the occurrence of the tumors throughout the gastrointestinal tract and in teratomas with gastrointestinal mucosal elements. Kultschitzky cells occur most abundantly in the mucosa of the appendix and ileum which accounts for the high incidence of tumors in these organs.

Kultschitzky-cell carcinomas comprise 90 per cent of all appendiceal cancers and 75 per cent occur in the distal third with less than 10 per cent of the tumors occurring in the base. Typically, this tumor grossly appears as a 2 or 3 cm. solid, bulbous swelling in the distal third of the appendix which on section is yellow, firm tissue. The lumen and architecture of the appendiceal wall is obliterated in the area of involvement [*11*].

Histologically, one sees small nests or large masses of regular epithelial cells occasionally forming gland-like patterns, with a total uniformity of cell and nuclear size and shape which is similar in all respects to the extra-appendiceal Kultschitzky-cell carcinomas (carcinoids) commonly held to have more malignant tendencies [*11*].

Diffenbaugh and others are impressed with the frequency of invasion of the submucosal, muscular and serosal layers of the appendiceal wall by these tumors. Despite this invasive tendency, giant cells, anaplasia and mitoses are virtually absent and, with only a relatively few cases of proved metastases from these appendiceal tumors, there is a general belief that these should be considered relatively benign. It is believed by some, however, that the benignity of appendiceal Kultschitzky-cell tumors is more apparent than real and, with identical growth and histologic characteristics, these tumors are as malignant as any. In most cases, obstruction of the small appendiceal lumen with subsequent

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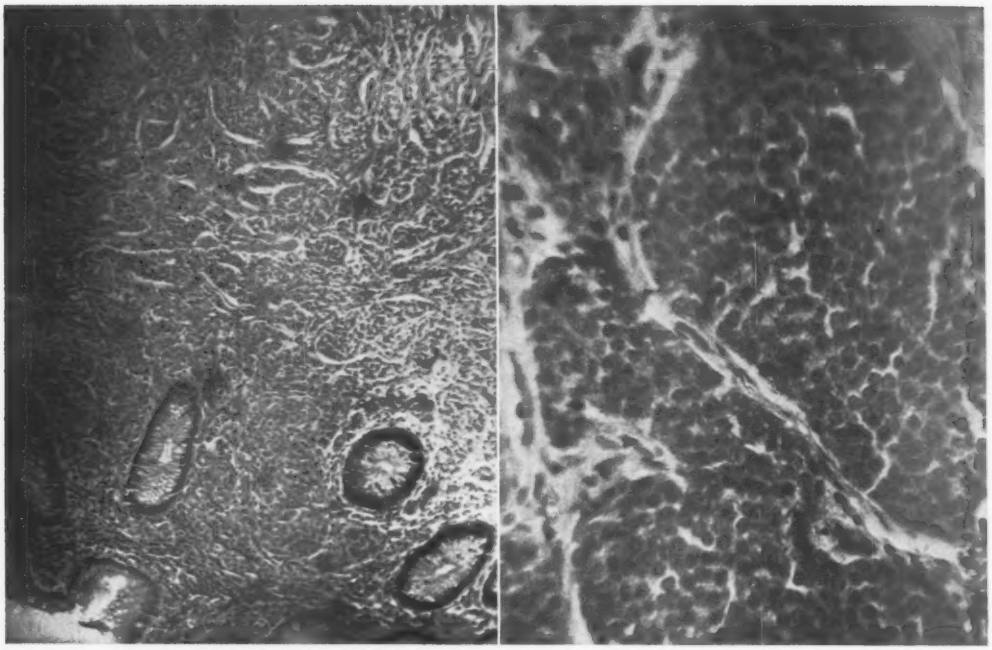

A B

FIG. 1A and B. Primary tumor in appendix.

inflammation leads to early surgery. Also, due to the vast numbers of appendixes removed electively incidental to other surgery, the appendix is removed prior to metastases which would occur if given time [5].

The average age of occurrence is twenty to thirty years, which is considerably younger than that in the Kultschitzky-cell carcinomas in other locations believed to be due to the same reasons as already mentioned. The tumors are more frequent in women, being quoted as 65 to 84 per cent in various series [5]. The youngest patient with this tumor with metastases found in the literature was a nineteen year old white woman reported on by Knowles et al. [8] in 1956.

The purpose of this paper is to report an additional case of Kultschitzky-cell carcinoma of the appendix with regional lymph node metastasis in a nineteen year old white man.

CASE REPORT

A nineteen year old white man was admitted on April 3, 1959, with a diagnosis of carcinoid of the appendix. On January 17, 1959, abdominal pain had developed and the patient was admitted to the station hospital at Port Lyautey where appendectomy was performed. He was found to have a carcinoid of the proximal third of the appendix which extended to the appendiceal stump. After an uneventful postoperative course, the patient was transferred to the U. S. Naval Hospital, Great Lakes, Illinois, for treatment and disposition. He was asymptomatic at the time of admission and past history and systemic review were noncontributory.

Physical examination was completely normal except for the recently healed scar in the right lower quadrant.

The initial studies including complete blood count, urinalysis, serology, stool examinations, chest roentgenogram, proctoscopy, upper gastrointestinal series and barium enema were within normal limits.

Review of the pathologic report and microscopic slide of the specimen demonstrated carcinoid cells extending to the serosal surface of the appendix and involving the most proximal portion of the specimen. (Fig. 1A.) Because of this, it was believed that the carcinoid had

probably involved the appendiceal stump which remained incompletely removed, and re-exploration of the patient was elected; however this was delayed due to an emergency leave.

Laparotomy through a right paramedian abdominal incision was performed on June 10, 1959. No liver nodules or enlarged lymph nodes were noted. There was considerable induration and thickening of the terminal cecum at the appendiceal site. An ileo-transverse colectomy with an end to end ileocolostomy was accomplished including removal of the mesentery of that portion of the intestine. The patient tolerated the procedure well and the postoperative course was completely uneventful.

Pathologic examination of the removed specimen showed the terminal ileum to be normal except for slight roughening of the serosal surface at the ileocecal junction. The cecum at the point of appendectomy and invasion was observed with many fibrous nodules, including bands. No mucosal abnormalities were noted. The cecal and appendiceal area was excised, fixed and prepared for multiple sections. Sections were taken of the pericecal nodes which totaled seven in number. Five nodes were found in the mesentery along the course of the ileocolic vessels and these were sectioned. The lymph nodes were small and soft. Microscopically there was no residual tumor at the previous operative site and no tumor found in the seven pericecal nodes. Metastatic carcinoid was found in the peripheral portion with some extension into the mid-part of one of the five nodes from the ileocolic mesentery. (Fig. 1B.)

A repeat barium enema postoperatively showed no evidence of obstruction or constriction at the anastomotic site and the visualized colon and small bowel appeared normal. The patient was discharged to be followed up at six-month intervals. The patient has remained well and asymptomatic one year postoperatively.

FIG. 2. Metastatic tumor in mesentery lymph node.

COMMENTS

It is believed that this case clearly fulfills the criteria set forth by MacDonald [*14*] for establishing malignancy in an appendiceal carcinoid in that the small intestine appeared normal, there was evidence of invasion of the appendiceal wall, no residual tumor at the stump of the appendix and definite evidence of metastatic tumor in a regional lymph node along the course of the ileocolic vessels (Fig. 2). It seems likely that this tumor had metastasized prior to the obstructive process leading to symptoms and surgery, since no residual tumor was found in the area of the appendiceal stump. The findings at operation and subsequent pathologic diagnosis show that metastases present in nodes may not be evident grossly at the time of surgery. Because of the slow growth of these tumors, routine five year follow-up study might well be inadequate to establish the fact that no tumor remains. This case would tend to strengthen the idea that invasion of the appendiceal wall should be considered as evidence of malignancy.

Although simple appendectomy is suggested by most, some surgeons have come to believe that if the diagnosis of a Kultschitzky-cell tumor of the appendix can be made at surgery, even though the tumor shows no gross evidence of spread beyond the serosa, radical surgery should be performed. Anlyan advocates right colectomy with eradication of lymph nodes draining the area [*4*]. Certainly, it is believed that these tumors should be subjected to complete and thorough microscopic examination, and if evidence of lymphatic permeation be found, the advisability of a right hemicolec-

tomy as for other malignancies with invasion should be seriously considered.

SUMMARY AND CONCLUSIONS

1. A brief review of "carcinoid" of the appendix is given.

2. The term Kultschitzky-cell carcinoma as first introduced by Eldred is recommended as a better, more descriptive term for all tumors now called "carcinoid" to establish and express the malignant potentialities of these tumors.

3. An explanation for the relatively low rate of metastases from the appendiceal tumors is re-emphasized as well as the malignant potentialities of these tumors with time.

4. A case report of a Kultschitzky-cell carcinoma with regional lymph node metastasis in a nineteen year old white man is presented.

5. A discussion is given including the criteria of malignancy and the fallacy of short-term follow-up study, and treatment is discussed.

6. Importance of careful and complete pathologic study is stressed.

7. It is believed that long-term follow-up study of patients with "carcinoid" of the appendix treated with simple appendectomy will eventually reveal cases of the so-called "malignant carcinoid syndrome" as a result of widespread metastases. It is believed, also, that many isolated cases of "carcinoid" of the appendix with metastasis have not been reported.

8. It is recommended that more importance be attached to the appendiceal Kultschitzky-cell tumors as concerns their microscopic study, long-term follow-up study and report of cases with evidence of metastases so that proper treatment will become more evident.

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Surgery Court Cases

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LANDSBERG VS. KOLODNY

District Court of Appeal of California

145 C. A. 2d 158, 302 P. 2d 86

The patient, who was pregnant, entered the Queen of Angels Hospital in Los Angeles, California. Upon admission the fetal heart beats suddenly dropped from 120/160 mm. Hg to a low of 80 beats per minute, a condition requiring immediate delivery. The patient was given a spinal anesthetic; the baby's head was found to be in an abnormal position requiring the use of forceps to rotate the head, resulting in certain lacerations. To facilitate delivery, the surgeon performed episiotomy to widen the vaginal canal, and to stop bleeding, inserted a number of cotton gauze sponges measuring about 4 by 4 inches square.

When the baby was born two loops of cord wrapped around its neck impeded breathing, which was restored by artificial respiration. Shortly after delivery, the patient suddenly had a severe hemorrhage, losing 3 or 4 pints of blood and indicating a failure of the uterus to contract normally; the patient's pulse rose, blood pressure dropped and it was feared that she would die on the table. After medicinal and other procedures failed to stop the bleeding, the surgeon packed the uterus with a 5 yard roll of gauze and then packed the vagina with a 3 yard length of gauze tied to the first roll. The hemorrhage was then arrested.

More than two years later, an exploratory operation by another surgeon disclosed a large abscess in the abdominal cavity. Within the abscess was lodged "an irregular mass of disintegrating gauze mesh," measuring approximately 7 by 6 by about 3½ inches. A second operation was performed during which the patient's spleen and three quarters of the stomach were removed. Many blood transfusions were required, and a third remedial operation was then performed.

The patient brought an action in the Superior Court of Los Angeles County against the surgeon to obtain damages for alleged negligence in causing the mesh of cotton gauze to become lodged and embedded in her abdomen. At the trial two theories were advanced as to how the gauze reached the patient's abdominal cavity. The expert witnesses suggested that in the packing process the fundus of the uterus was accidentally punctured and a portion of gauze was shoved through the opening. The other explanation was that one or more gauze sponges, used to wipe away bleeding caused by lacerations or incisions, passed through cervical or vaginal lacerations into the cul-de-sac close by and were carried into the abdomen. A jury returned a verdict in favor of the surgeon and the court entered judgment accordingly. The patient appealed.

The District Court of Appeal of California affirmed the decision of the court below. The District Court of Appeal declared: " . . . under either theory . . . the jury may have reached the conclusion that the occurrence was in the category of an unavoidable accident."

* Counsellor at Law of the Supreme Court of the United States of America.

HUTTNER VS. MACKAY

Supreme Court of Washington

48 Wash. 2d 378, 293 P. 2d 766

The patient suffered a generalized convulsion, and his condition was diagnosed as a low level of epilepsy. The following year, he suffered another convulsion of the same type. Two years later, he contracted a cold which was accompanied by severe headaches. Thereafter, he suffered diplopia in one eye and consulted an ophthalmologist, who examined his eyes and changed the lenses in his glasses. When the diplopia continued, the doctor sent him to consult an eye, ear, nose and throat specialist. This doctor reported that the trouble did not stem from the ears, nose or throat, and referred the patient to a surgeon.

After the doctor-patient relationship was agreed upon, the patient gave the surgeon a history of his subjective symptoms. The history included a negative Wasserman test. An electroencephalogram indicated that there was some generalized cerebral dysfunction and a grade 2 focal lesion in the right frontal lobe. The surgeon's examination of the patient also disclosed an incipient choked disk in the right eye. Roentgenograms taken earlier by another doctor showed a normal skull.

A pneumoencephalogram was performed. During this diagnostic study, the manner in which the fluid flowed from the spinal canal indicated that the patient had high intracranial pressure. The roentgenograms taken were negative for abnormalities. A ventriculogram was performed. The roentgenologist reported that these roentgenograms were negative for abnormalities. However, the roentgenograms confirmed the surgeon's clinical diagnosis that the patient was suffering from a deep-seated brain tumor in the right frontal temporal area. On the same day, the surgeon performed craniotomy.

During this operation, the surgeon cut a portion of the patient's skull. When the bone was laid back, approximately 15 square inches of the dura was exposed. The surgeon put several "nicks" in the dura and inserted a cannula in different places in an attempt to locate the tumor. When the surgeon did not locate the tumor in this manner, he incised the dura. Because of the intracranial pressure, this incision allowed the brain to herniate through the opening in the skull. The herniation was in the general area of the motor-sensory cortex. Thereafter, the surgeon cannulated further, but could not reach the tumor. He closed the opening, leaving the skull flap slightly raised to compensate for the intracranial pressure. The damage resulting from the herniation caused paralysis of the patient's left side. He was discharged from the hospital. Thereafter, on several occasions, the patient was seen by the surgeon in his office. The surgeon prescribed certain medicines during these calls, and over the telephone.

Later, the patient was in Harborview Hospital in Seattle, Washington, with pneumonia. While there, he was visited by a second surgeon, who became interested in the patient's condition. The second surgeon completed an extensive diagnostic examination. His diagnostic studies did not reveal the exact location of the tumor or whether it was operable. He received permission to perform an exploratory operation. He operated through the same opening in the skull as had the first surgeon. After incising the cortex, he discovered a tumor in the base of the right ventricle and removed a small piece of it. This operation resulted in decreased intracranial pressure, thus permitting the herniated portion of the brain to recede so that the skull flap could be replaced in its normal position. The second surgeon performed a second craniotomy. This time he operated from a different angle, approached the tumor from the bottom and removed another piece of it.

Subsequently, a third operation was performed, whereby tubes were inserted so that the excess fluid around the brain could drain through the ears and throat into the stomach, where it would be re-absorbed.

Although the operations performed by the second surgeon relieved the pressure on the patient's brain, the tumor was inoperable and could not be completely removed. Therefore, the operations were palliative only and did not correct the paralysis.

The patient filed an action in the Superior Court of King County, Washington, against the first surgeon to obtain damages, alleging that the surgeon had performed an exploratory craniotomy when only a craniotomy to remove the tumor had been authorized. At the trial testimony established that a craniotomy had been authorized. However, the patient's wife

testified that she had not authorized an exploratory craniotomy. The surgeon did not testify that he performed an exploratory operation for diagnostic purposes. He used the term "exploratory" generally, in that, in his opinion, all operations are exploratory because the practice of medicine is not an exact science. He testified that, from his diagnosis, he concluded that the tumor was located in the right frontal temporal region, but the operation disclosed it was too deep-seated for removal. He admittedly was authorized to remove the tumor. The evidence established that its exact location, or if it was operable, could be determined only by a craniotomy such as the surgeon performed.

The court dismissed the case, and the patient appealed. The Supreme Court of Washington sustained the decision of the lower court. The Supreme Court stated: "Where a doctor is authorized to remove a tumor by means of a craniotomy and finds, during the operation, that it cannot be removed without grave risk to the life of his patient, the authority to remove the tumor carries with it the implied authority not to do so when death would be a most probable result. The doctor performed the operation authorized."

Our Surgical Heritage

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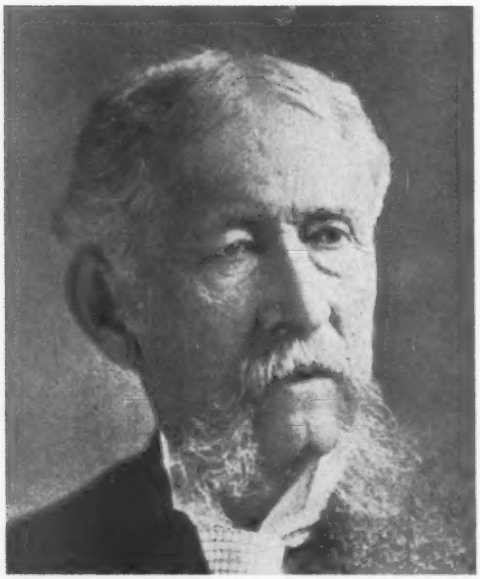
UNITED STATES OF AMERICA



DAVID W. YANDELL

DAVID W. YANDELL, surgeon and educator, was born September 4, 1826 in Craggy Bluff, Tennessee. His father was the eminent Lunsford Pitts Yandell, who for many years graced the faculty of Transylvania Medical School and later the University of Louisville. His mother was Susan Wendel of Murfreesboro, Tennessee.

Dr. Yandell received his early education in the bluegrass region of Kentucky in "classic Lexington" after which he attended Centre College of Kentucky at Danville. He began the study of medicine with his father as his preceptor and graduated from the University of Lousiville with an M.D. degree in 1846. He was a graduate student in Europe during 1847 and 1848, and it was during this period that he wrote two series of letters: one was published in the *Louisville Journal* and the other was published in the *Western Medical Journal.* The letters were delightful reading and full of

facts, common sense and philosophic comment. They are classics in the literature of American surgery.

In 1849, Dr. Yandell returned to Louisville and joined his father Dr. Lunsford Pitts Yandell in the practice of medicine. He was made demonstrator of anatomy in the University of Louisville and as such he acquired an intimate knowledge of the human anatomy which made him particularly deft and sure of hand which later marked his surgical career. In 1854, he was made Professor of Clinical Medicine at the University of Louisville, but this was rather short lived owing to the American Civil War. Casting his lot with the South, he enlisted in the Confederate Army and was attached to the armies of General Hardee and Joseph E. Johnston and was in the battles of Shiloh, Murfreesboro and Chickamauga. He was made Medical Director of the Department of the West under General Albert Sidney Johnston and served with distinction until the end of the War.

At the University of Louisville he was an assistant to and Chief-of-Clinic for the esteemed Samuel D. Gross from 1848 to 1856, and it was during this period that he established the Stokes Free Dispensary with outpatient teaching. This was the first outpatient clinical institution west of the Alleghenies. His high regard for the great master Samuel D. Gross was shown on many occasions. It was said that Dr. Gross and Dr. Yandell, master and pupil, "were lovely and pleasant in their lives," and it was also said that they were like Saul and Jonathan, "they were swifter than eagles; they were stronger than lions." Dr. Yandell was Professor of Surgery at the University of Louisville from 1869 to 1898.

His one great contribution to American surgery was the classic "The Report and Analysis of 415 Cases of Tetanus." He founded and served for many years as Editor of *The American Practitioner*, which was one of the most classically edited and best known periodicals in the United States during its period of publication.

In 1871, he was elected President of the American Medical Association and presided with such aplomb that Dr. Bowditch of Boston expressed the wish that he be made President for life. David Yandell was President of the American Surgical Association in 1889 and founded the Louisville Surgical Society in 1890. He died May 2, 1898 of arteriosclerosis at his home in Louisville which had been his and his father's since 1848.

David W. Yandell was a good fighter and a fair hater. He could give and take hard blows, but he could love with a great heart which had a constancy that knew no change. It is said that he operated with geometric precision and was *the* surgical teacher west of the Alleghenies. He was a most vigorous, original and versatile figure.

EUROPE

ROBERT LAWSON TAIT

LAWSON TAIT, originator of the Staffordshire knot, was born in Edinburgh, Scotland in 1845. He received his early education at Heriot's Hospital School and later was a student at the University of Edinburgh. He became a licentiate of the Royal College of Surgeons of Edinburgh in 1866, and in 1870 was made a Fellow of the Royal College of Surgeons of Edinburgh. Mr. Tait was made a Fellow of the Royal College of Surgeons of England in 1871. He was an intern for three years in a hospital in Wakefield, and in 1870 established himself in Birmingham, England. Tait was active in the establishment of the Birmingham Hospital for Women and was appointed the first surgeon to this institution. He conducted his own private hospital, named The Crescent, which was connected to his home.

He was dexterous in his operative work and seldom took over three minutes to repair the perineum. He performed all abdominal sections with a three inch incision just to the left of the midline; his rule was never to extend it beyond that limit unless the abdominal tumor was of great size. Tait could never align himself with Lister's theory of antisepsis, but he emphasized the necessity of cleanliness in all operative procedures which is probably his greatest contribution to surgery for he was really the forerunner of surgical asepsis. His axiom was quoted around the world: "the time to cure peritonitis is before it begins." Although many of his confreres were using the carbolic acid spray in the operating room Tait would never let it be used. Instead, he depended on scrupulous practices of cleanliness such as the boiling of instruments and the scrubbing of the hands and abdomen with soap; his results were better than those of surgeons who used the spray.

It is said that he was the first to remove gallstones, one of the first to operate in cases of ruptured ectopic pregnancy and the first to remove uterine appendages to relieve the bleeding of fibroid in the uterus.

In 1873, Tait published the treatise *Diseases of the Ovaries*, and in 1879 a book entitled *Diseases of Women*. The paper, *A General Summary of Conclusions from 4,000 Cases of Abdominal Section*, which he published in 1894 did much to stir the surgical world.

Tait was an inventive surgeon. He devised a special operation for excision of the fallopian tubes and ovaries by ligating the pedicle with a silk ligature tied with a knot; this method which he originated has since been called the Staffordshire knot.

Lawson Tait underwent surgery for removal of a renal calculus; he was never well thereafter. He died on June 13, 1899 as a result of uremia. It was no coincidence that his last medical paper was entitled *The History of a Sore Kidney*.

The world especially England and America, because of the many surgeons who had visited his clinic, lost a great surgeon. "He who was gentle and delicate in manner but when vexed could roar like a lion. He was one of the most tender-hearted men in English surgery."

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